# PROCEEDINGS

OF THE

# NEW YORK PATHOLOGICAL SOCIETY

NEW SERIES, VOLUME XXI

1921


ORGANIZED IN 1844

INCORPORATED IN 1886

NEW YORK
1921

PRESS OF
THE NEW ERA PRINTING COMPANY
LANCASTER, PA.

# Proceedings

of the

# New York Pathological Society

New Series, Vol. XXI JANUARY-MAY, 1921 Nos. 1-5

CONTENTS



DR. DOUGLAS SYMMERS, *President*

# THE BACTERIOPHAGE REACTION OF D'HÉRELLE

ABRAHAM ZINGHER, M.D.

The interesting studies published during the past three years by d'Hérelle,[1] Kabeshima,[2] Salimbeni,[3] Bordet and Ciuca,[4] Gratia,[5] and Maisin[6] have drawn our attention to an agent that seems to have an important function in the destruction of the intestinal bacteria and in the recovery from the diseases included in the typhoid-dysentery group. Such a bacteriophagic agent was originally described by Twort[7] in the *Lancet,* 1915, in connection with observations on *staphylococcus* cultures derived from glycerinated vaccine virus, and on *coli* cultures from the intestinal tract of dogs suffering from distemper. Similar observations were also made by him on a large bacillus obtained from the intestinal tract of children suffering from diarrhœa.

The agent is described by d'Hérelle as a filterable virus which grows upon and destroys the pathogenic bacteria with which it is associated. It is found toward convalescence in the intestinal diseases, is not absolutely specific, and can be cultured indefinitely in series by transplanting a fraction of a loopful of the lytic fluid into fresh suspensions of the bacteria in bouillon.

These observations were first carried out by d'Hérelle in connection with the Shiga dysentery and then extended to the other types of dysentery, to typhoid, paratyphoid, and fowl typhoid.

Kabeshima does not consider this agent as a living virus, but as a ferment derived originally through the action of a leucocytic catalyzer upon the bacteria, causing the liberation of a ferment which can continue to act indefinitely in series of fresh suspensions of the organism.

Salimbeni's observations indicate that we are dealing with a myxameba-like organism which has two stages—a filterable spore stage and a vegetative fungus stage. These observations are probably erroneous. The appearances, which he describes, are probably artefacts developing during different stages of lysis of the bacteria.

More important, however, in explaining the nature of this agent is the work of Bordet and Ciuca, who consider that this lytic power is an hereditary lytic property produced by the action of leucocytic ferments upon bacteria, some of which subsequently acquire a property of being lytic for the original strain from which they were derived. Bordet and Ciuca obtained the lytic agent by the injection of a *B. coli* strain into the peritoneal cavity of guinea pigs. The action of this lytic peritoneal exudate upon the original strain showed up colonies of the *B. coli* which were resistant to lysis and very mucoid and translucent in appearance. The bacteria of this "modified" strain of *B. coli* were actively motile, resistant to the action of the lytic agent, and much more pathogenic for guinea pigs than the original strain. These "modified" bacteria have acquired the property of producing inhibition of growth and lysis of the original strain. This property is preserved through later generations and represents a new biological function of the bacteria.

One of Bordet's co-workers, Gratia, has shown more recently that in an old and evidently dead culture of the Bordet strain of *B. coli* small colonies were found that were markedly resistant to ageing. Upon transplantation these colonies proved to have the same resistant properties to the lytic agent as those of the resistant strain obtained directly by the action of the lytic fluid upon the original strain of *B. coli*. These studies, according to Gratia, seem to have an important bearing upon the questions of virulence, the heredity of acquired characteristics, and the formation of new races.

Through the kindness of Dr. Hardé, who brought specimens of lytic fluid from d'Hérelle to this country and placed them at my disposal, I was able to make some studies on the nature of this agent. The pressure of other work has prevented me from continuing these most interesting studies, and I can only submit the following limited observations:

One specimen marked "Bateriophage anti-Shiga," dated May 19, 1919, produced inhibition of growth in a fresh suspension of the Shiga bacillus and caused lysis of bouillon cultures grown

24 to 48 hours. Subcultures were sterile. A trace of this new lytic fluid showed the same property toward fresh bouillon suspensions, which in turn exerted the same powerful lytic action, which could be continued on indefinitely in series.

By great dilution the action of this lytic agent was diminished. In place of the complete inhibition of growth on the agar subcultures which were made immediately after the addition of the diluted lytic fluid to a fresh suspension of *B. Shiga,* a surface growth developed which showed here and there circular depressions with no growth surrounded by a halo leading off into the growth. These circular depressions were considered by d'Hérelle as representing colonies of the bacteriophage, by Gratia as the evidence of the lytic action of products of the resistant bacteria upon the non-resistant bacteria.

By making agar plates of the Shiga bacillus and streaking the surface crosswise with a loopful of the lytic fluid I could observe the following day a complete area of clearing along the path of the streaked lytic fluid which was surrounded by a regular surface culture of the Shiga bacillus. Studying the margin of the clear area, I noticed that the culture of the Shiga bacillus had at this point a shelving edge where it was quite translucent, and which upon microscopical examination showed the presence of most interesting structures. There was first a fine granular background, representing probably detritus derived from the bacteria; second, long, slender, refractive crystals, singly or in small groups of two and three; third, numerous irregular structures, not motile, pentagonal or hexagonal in shape, or of an irregular round form, which stood out clearly against the granular background. These bodies resemble closely in size and appearance crenated red blood cells. They could be floated in a hanging drop and seemed to have a somewhat spherical shape. They could be stained with Giemsa and less clearly with Gram's stain in ordinary preparations and in preparations made by impression from the agar plate. In the stained preparations the structures appeared as amorphous non-nucleated masses. It is probable that these structures represent *hyaline masses of protoplasm* resulting

from the action of the lytic agent upon the bacteria. Here and there along the margin of the streak small circular indentations could be seen in the culture proper which corresponded closely in appearance to the colonies of bacteriophage described by d'Hérelle. The microscopical examination of the margins of the circular areas showed numerous structures similar to those described above—granular detritus, refractive, slender crystals, and irregular protoplasmic hyaline bodies. The more central part of the clear streaked area showed in places upon microscopical examination similar structures.

After two to three days there appeared in the clear area small colonies which upon transplantation grew with difficulty. On the agar plates the subcultures of these resistant colonies did not show the above-described structures which indicate the action of the lytic agent upon non-resistant bacteria.

The specificity of the lytic fluid was also studied. It was found to completely inhibit a second strain and only partly inhibit a third strain of *B. Shiga,* and to produce complete inhibition of a Flexner-Harris and a Mt. Desert strain of dysentery bacilli. It had no action upon a typhoid strain (Pfeiffer), *B. coli, B. sanguinarium,* and paratyphoid A and B.

Microscopical studies of hanging drops made according to the method described by Salimbeni gave no evidence that we are dealing with a myxameba. The irregular hyaline structures described previously showed no motility. The lytic agent was found to produce very active and almost instantaneous agglutination of bacteria.

The lytic agent resists the temperature of 70° C. for one half hour, but is partly destroyed by a temperature of 75° C. for one half hour.

Studies were also made with the anti-typhoid bacteriophage sent over by d'Hérelle. On the agar plates inoculated with the *B. typhosus* (Pfeiffer) and streaked crosswise with a loopful of the lytic fluid, structures similar to those described above were found along the margin of the culture and within the cleared area.

The anti-typhoid lytic fluid produced complete inhibition and

lysis of the *B. typhosus* (Pfeiffer). It also produced complete inhibition and lysis of the Flexner-Harris and Shiga dysentery strain, but only partial inhibition and lysis of paratyphoid A and B strains, of five recently isolated typhoid strains, and of the Mt. Desert strain, and no lysis of the *B. coli* and *B. sanguinarium* strains.

A third bacteriophage against the *B. sanguinarium* was also studied. Structures similar to those described in connection with the anti-Shiga and anti-typhoid bacteriophage were also seen on plates inoculated with the *B. sanguinarium* and streaked crosswise with a loopful of the anti-sanguinarium lytic fluid. The lytic agent produced complete inhibition and lysis of three different strains of *B. sanguinarium,* of the Shiga strain, and of the typhoid (Pfeiffer) strain.

The foregoing short studies indicate that these lytic agents are not *absolutely specific* for their own bacterial strains. They also indicate that we can recognize the *lytic action* of these agents upon bacteria by the *curious irregular but sharply defined and prominent structures which are found on agar plates at the point of contact of the lytic agent and the bacterial culture—long, slender crystals and protoplasmic hyaline bodies.* A few small colonies developed slowly within the clear area on the streaked agar plates. Subcultures on agar showed that they were *resistant* to the action of the lytic agent. This was also seen when the lytic agent was added to fresh suspensions of these bacteria.

*Bibliography*

1. D'HÉRELLE, F.: *Compt. rend. Acad. d. sc.,* 1917, clxv, 373; 1918, clxvii, 970; 1919, clxviii, 631.
D'HÉRELLE, F.: *Compt. rend. Soc. de biol.,* 1918, lxxxi, 1160; 1920, lxxxiii, 52, 97, 247, 1318, 1320; 1921, lxxxiv, 339, 384, 538, 719, 863, 908.
2. KABESHIMA, T.: *Compt. rend. Soc. de biol.,* 1920, lxxxiii, 219, 471.
3. SALIMBENI: *Compt. rend. Soc. de biol.,* 1920, lxxxiii, 1545.
4. BORDET AND CUICA: *Compt. rend. Soc. de biol.,* 1920, lxxxiii, 1293, 1296; 1921, lxxxiv, 276, 278, 280, 745, 747, 748.
5. GRATIA, A.: *Compt. rend. Soc. de biol.,* 1920, lxxxiv, 275, 750, 751, 753, 755; 1921, lxxxv, 25. *Jour. Exper. Med.,* 1921, xxxiv, 115.
6. MAISIN, J.: *Compt. rend. Soc. de biol.,* 1921, lxxxiv, 467, 468, 755, 847.
7. TWORT, F. W.: *The Lancet,* 1915, ii, 1241.

*Discussion:*

DR. WILLIAMS: I have followed Dr. Zingher's work with a great deal of interest. The macroscopic appearance in these plates of rounded chewed-out areas is very similar to the appearance that can be obtained when inoculating amebas with cultures of suitable bacteria, such as *B. dysenteriæ* or *B. typhi.* But under the microscope these appearances are nothing like those of any amebas I have ever seen. These small ameboid-like bodies look much more to me like broken down products than like living organisms.

DR. PARK: This paper deals with a subject which is both most interesting and most difficult of understanding. I think it must appear to all of us that it is almost impossible to conceive that the results are due to ferments alone since we do not know anything about a ferment which may increase. Again the idea that a microorganism would suddenly so change its function as to make a ferment which would attack the strain from which it had lately developed is something that we have never come across, so that naturally the newest hypothesis of Salimbeni that there is a parasite growing on the organism appealed very much to us. This theory has its own difficulties. If the parasitic fungi exist there must be a number of these. We are exploring in a new field which is very interesting. It is hazardous at the moment to say more than that.

MISS KUTTNER: I have been able to isolate a lytic principle similar to that described by d'Hérelle from a typhoid stool sent to me through the courtesy of the Health Department. It corresponds to practically everything d'Hérelle has described. It is non-specific; it acts on the homologous typhoid strain and on the other typhoid strains, as well as on Shiga and Mr. Desert dysentery bacilli. It has no action against paratyphoid A or B, or against *B. coli.* It is both inhibitory and lytic. I have not found that cultures dissolved or inhibited by this lytic principle remain sterile indefinitely as described by d'Hérelle. If cultures which have been acted upon by the lytic principle are plated after several days two types of colonies develop, one the typical round typhoid colony, the other irregular. The irregular colonies are often quite jagged and triangular, and if transplanted into broth do not make the broth turbid, whereas a normal colony from the same plate does, and furthermore, the lytic principle is also transmissible from one of these colonies fished into broth, that is, starting with a fishing of one of these triangular colonies in broth, the lytic principle can be transmitted in series in the same way as from the original stool filtrate. I would like to ask Dr. Zingher how he reconciles the theory of the ultra-microscopic spore with the fact that a single brief contact with this lytic principle changes the organism so as to give two types of colonies from one of which it is possible to transmit the lytic principle in series. For instance, if a small amount of the lytic principle I have isolated from a typhoid stool is added to a young turbid broth culture of typhoid, Shiga or Mt. Desert, and sub-cultures are immediately made, it will often be found that the two types of colonies, the normal and the lytic, will be obtained. I cannot understand how a single short contact with the lytic principle in this

way, which produces such an immediate and profound change in the cultures of three different organisms such as typhoid, Shiga and Mt. Desert, can be attributed to the action of a fungus.

DR. JOBLING: It is difficult to assign the phenomena described by Dr. Zingher to the action of either bacteria, fungi, or antibodies. The fact that Bordet was able to obtain a similar agent from bacteria after their injection into the peritoneal cavity of a guinea-pig complicates matters. Is the agent producing the lysis a normal inhabitant of the peritoneal cavity, or was Bordet fortunate in his choice of a guinea-pig? Are we to assume that there is in the intestine a specific substance, or organism, for each type of bacillus; or are we to believe that the agent exists free in the intestine, with the ability to become attached to any organism after which it cannot grow except in symbiosis with that particular organism?

DR. ZINGHER: I have not been able to confirm the observation of Salimbeni as regards the myxameba-like structures which he has observed in wet slide preparations of bacterial suspension and lytic agent. The small, highly refractile bodies which he describes in hanging drops of a freshly made preparation of bacteria and lytic agent seem to be simply the ends of bacteria, which are seen in a vertical instead of a horizontal position. I have noted the two types of colonies of which Miss Kuttner spoke. The irregular colonies show upon microscopic study the structures characteristic of the action of the lytic agent upon the bacteria—the long slender crystals and the sharply defined irregular hyaline masses.

## CUTANEOUS REACTIONS IN HUMAN HYPER-SENSITIVENESS

ROBERT A. COOKE, M.D.

*(From the Department of Immunology of Cornell University and the New York Hospital, First Medical Division)*

The two main points that I shall discuss with you regarding the cutaneous reaction in human hypersensitiveness are first the method of making the test and secondly the significance of the local reaction.

1. *Method of Testing:* Cutaneous tests can be made by the abrasion method when the substance to be tested is applied in dry form or as an extract, or by the intradermal method when a solution or extract is introduced into the skin by means of a fine hypodermic needle.

Dr. Brown has been making some very careful duplicate tests with these two methods in our clinic, and since time will not permit a detailed statement, I shall only say that the results warrant the conclusion that the intradermal test is by far the more delicate and gives definite positive results to agents definitely proven to be productive of clinical symptoms when the abrasion test, using these same agents, is absolutely negative. What follows has to do entirely with results from the use of the intradermal test and our own preparations.

2. *Significance of the Cutaneous Reaction:* The *local reaction* divides itself into three groups, (1) the immediate reaction, (2) delayed reaction, (3) negative. The *immediate reactions* are marked, moderate or slight. Marked reactions are characterized by the appearance of an urticarial wheal with pseudopod projections and a surrounding zone of hyperemia, appearing in ten to fifteen minutes. Moderate reactions lack the pseudopod projections and do not form so large a wheal. They have a hyperemic zone. The slight reactions show a hyperemic zone with little or no increase in the wheal. Slight and moderate reactions are at times obtained to extracts in a very weak solution and become marked where more concentrated solutions are tried. Where reactions are slight or moderate to the concentrated extracts they are dismissed as of no clinical significance unless they go on to develop delayed reactions and fall then into a different group to be discussed later.

Marked reactions are of the greatest importance, but they, too, are occasionally false. At times one gets what we call the "splash" reaction, when the point of the needle happens to lie between two easily separated layers of the derma or epiderma, and the extract seems to splash out at once into an area with irregular edges. In such cases the wheal looks like a marked positive reaction, but it lacks the hyperemic zone. This also happens when an air bubble is introduced by mistake. Then occasionally, but not frequently, a definite marked positive reaction is obtained, which can never be verified. These, too, must be set aside as of no clinical significance, for they could only indicate a

short fleeting phase of allergy, a clinical condition of which we are not as yet cognizant. But marked positive reactions occurring on repeated testings always indicate a true hypersensitiveness. This statement requires a reservation, or more truly an explanation, in order not to be misleading. Cutaneous hypersensitiveness does not necessarily indicate clinical hypersensitiveness, because in the ordinary course of life the allergen can never be brought in contact with the hypersensitive cells. Let me cite briefly two actual cases to illustrate the point:

The first is the case of a man forty-five years old who had been troubled for five years with a very extreme degree of vasomotor rhinitis, so-called. He gave marked cutaneous, ophthalmic and nasal reactions to corn and cottonseed meal. On the strength of this reaction one might have been tempted to withdraw corn and cornmeal from his diet. But it so happened that five years before this man had retired to a little farm and took great pride in his chickens which he fed himself religiously twice a day with corn and cottonseed meal. As soon as he stopped this his vasomotor rhinitis stopped. He was able to eat corn and cornmeal which he did freely as a test without the slightest trouble. An injection of extract of corn produced a constitutional reaction with coryza and cutaneous hyperemia and urticaria. This case also illustrates the dangers in the interpretation of positive reactions when applied to foods.

The other case is that of a woman thirty years of age who had never had hay fever of the early type, in May and June, and would have recognized it before because she had autumnal hay fever for about fifteen years. The test with a timothy pollen extract in March was markedly positive. That following June she had perfectly typical clinical hay fever of the early type.

We now have records of several such cases giving marked positive cutaneous reactions with negative ophthalmic reactions. Such cases we consider as potential hay-fever cases. They have no clinical symptoms because the mucous membranes have not become hypersensitive. But we have had the satisfaction of watching such cases develop clinical hay fever at a later date, at which time the mucous membranes react positively. Aside from the inheritance factor, such an experience tends to make one feel that the constitutional reaction is developed within the body by some means other than ordinary immunological procedure adopted in animal anaphylaxis.

*Delayed cutaneous reactions* occur from six to twenty-four hours after the test and are characterized by an area of edema and redness, usually with itching, sometimes only an inch or two in diameter, and at others extending to the elbow or even wrist when injection is made in the upper third of the arm. Of the clinical significance of such reactions nothing definite can be said at the present time. They are usually obtained with the food extracts rather than pollen extracts, and may occur in apparently normal individuals or in those with clinical asthma, urticaria or angio-neurotic edema; but so far as we can determine, foods giving such reactions may be eaten with impunity. We have never yet been able to make and prove a diagnosis on the basis of a delayed reaction, no matter how severe.

*Negative Reactions:* At the site of the test there is no enlargement of the papule caused by the injection of the 1/50–1/100 c.c. of the extract tested. There is no hyperemia or other evidence of cellular or vascular activity either immediate or delayed. In general such tests indicate absence of hypersensitiveness, at least in the skin. But in exceptional cases negative reactions occur when the clinical history is absolute and definite. We have seen a number of cases with a history of acute and severe abdominal pain, vomiting and diarrhœa, occurring about twenty minutes after the ingestion of clam. It has occurred not once, but several times. The cutaneous reaction is always negative. Such cases can readily be explained on the basis of a localization of the hypersensitive area to the gastric or upper intestinal tract. We have observed this same localization of hypersensitiveness to the nasal mucous membrane in a very few cases of vasomotor rhinitis, and not infrequently in hay fever the degree of hypersensitiveness is much greater in one eye than in the other.

Just as we see local reactions of the immediate and delayed type, so also do we see immediate and delayed clinical reactions. By delayed clinical reactions I mean a reaction occurring twenty-four hours to five days after the ingestion of a substance. Immediate local reactions, when they signify anything at all, indicate an immediate clinical reaction, but delayed local reactions are

not indicative of delayed clinical reactions; in fact, they have no known significance.

Time has not permitted me to go extensively into details nor to give statistics on the relative frequency of the exceptions to the rule. Suffice it to say that the application of the test to the diagnosis of clinical condition must be made with the greatest care, and we make it a rule for the absolute diagnosis of a specific etiologic factor to conform to the following commonsense requirements, which we have dignified by the term postulates:

1. Hypersensitiveness must be proven either by:

(*a*) A local reaction of a marked type that can be verified at will, or by

(*b*) A constitutional reaction that duplicates the clinical condition under study when the allergen is introduced by ingestion, inhalation, or by intradermal, subcutaneous, or intravenous injection.

2. It must be proven that the individual comes in contact with the reacting substance in such a way that it can be responsible for the clinical condition.

Dr. George M. Mackenzie read a paper entitled "The Relation of Antigen and Antibody to Serum Disease Susceptibility and Insusceptibility," which appeared in *The Journal of Experimental Medicine*, 1921, xxxiii.

*Discussion:*

DR. LONGCOPE: I have naturally been very much interested in this work of Dr. MacKenzie's. Serum disease, which is really a characteristic example of an acute infectious disease, offers a beautiful opportunity to study certain phases of the relationship of an infecting agent to antibody formation in a condition where the cause of the disease is not a living agent, but one with physical properties only. For protein is not a living agent. The experiments which Dr. MacKenzie has described I think offer very good evidence that there is an essential difference between the susceptible individual and the insusceptible individual to this disease produced by the non-viable substance, horse-serum—that the susceptible individual does readily produce antibodies and precipitins, whereas the insusceptible individuals are not likely to produce antibodies, while in them the antigen, the horse-serum, continues to circulate as a perfectly innocuous substance for long periods of

time. Dr. MacKenzie has discussed the possible explanation for these phenomena. I do not think there is any evidence to show that one explanation is better than another, but any observations or any data that can be brought to bear on the subject of individual susceptibility to disease are most important, and for that particular reason possible analogies are interesting, though it may not be proper to draw analogies for acute infectious diseases from these experiments.

In regard to Dr. Cooke's interesting observations, I am sure that Dr. MacKenzie has noticed that the intradermal tests were much more delicate than the dermal tests. Walker has ruled out the intradermal test, saying that it is difficult to read. I do not believe that there is any great difficulty in this regard, if the tests can be done with materials that are sufficiently diluted.

Dr. Cooke's observations on the reactions in the skin and in the mucous membranes, and their variation in the same individual to the same substance, are very interesting. We have noticed this a number of times, and I recall one man in particular who gave skin reactions to a great variety of substances. He was perfectly well when he was in the hospital, but whenever he left the hospital he was likely in a short time to have such a violent attack of asthma that he would be picked up in the street and taken to the accident ward of a hospital as a medical emergency. Among other things he gave a marked reaction to rabbits' serum, though he was perfectly certain that no animal ever gave him attacks of asthma. He said he could pet a rabbit and do anything he wanted to with it without danger of asthma. We took him into a room where a rabbit was. He touched the rabbit with his hand. Almost immediately he had an urticaria of the hand, and for a week subsequently he suffered from a terrific attack of asthma. Though he gave the same skin reaction to various other animal sera, he could be fed enormous quantities of dried serum without any disturbance whatsoever.

Another interesting thing is the varying degree of hypersensitiveness which great groups of individuals show. I have no doubt that if one selected a hundred or a thousand perfectly normal individuals that a good many of them would either give delayed or immediate reactions to certain protein substances. I give reactions to a certain number, and I have never had any symptoms from eating or coming in contact with any of these materials. There must be a variation in groups of individuals from those who are hypersensitive and who have symptoms which can be accounted for by this curious condition, through individuals who are rarely affected and finally to individuals who are perfectly normal, though still presenting evidences of hypersensitiveness when tested appropriately.

A confusing thing in interpreting the skin reaction is the frequency of multiple reactions. People who do have urticaria, asthma, etc., may react to a long series of substances, and we have seen a number of individuals who give extremely marked reactions to extracts of animal hairs, and yet in whom it is evident that the asthma is not brought on by inhalation of dust from these animals. I recall one boy in particular. From the strongly positive test we assumed that it was due to contact with some

animal, until we discovered from his mother that she thought eggs had something to do with it. He gave no reaction to eggs, by the ordinary tests, but when given large quantities of egg intradermally, he did give a fairly marked reaction to it, and when eggs were removed from his diet, he recovered and has remained perfectly well for several years, except for one or two attacks following the ingestion of eggs. This is simply an illustration of the difficulty of analyzing the significance of skin reactions when many positive tests are obtained.

DR. HUNTOON: I think from Dr. MacKenzie's paper that he does not make a distinction in classification between those people who give immediate reactions, and who give typical serum disease which comes on five to twelve days after the injection of the serum. I believe he stated that the hypersensitive cases stood at one end of the line, and the cases that give no reaction at all at the other, and there are all gradations in between. If this hypothesis is true that these two classes of symptoms belong in the same class, then these individuals should show a considerable amount of precipitin in their blood before the serum is injected, and in that event the cases that give extensive immediate reactions with small amounts of serum would later show a typical serum disease. I wish Dr. MacKenzie would inform me on these points.

DR. PARK: I was going to ask Dr. MacKenzie concerning the point brought up by Dr. Huntoon. Dr. Cooke's observations seemed to indicate a difference in significance between the early and late reactions, while those of Dr. MacKenzie seemed to class them together. His observations are of great interest and value, even if his interpretation of their meaning may later have to be modified. Dr. MacKenzie attributes the serum reaction largely to the patient's characteristics. I wonder how he explains the differences in the sera from different horses. Most sera used in treatment are mixtures from different horses. In order to estimate the individual characteristics we used individual horse serums and found the serum from some horses gave very different reactions from that from others. I remember that No. 83 gave about sixty per cent. of scarlitiniform reactions and had to be discarded. There is certainly a marked difference in the sera as well as in the patients. Realizing that proteins giving the therapeutic effects were not necessarily deleterious, we tried to modify or select the serum so as to avoid the unnecessary reactions such as the immediate chill following an intravenous injection. We have met with some peculiar as well as interesting results. We found for instance that we had a slightly turbid antitoxin globular preparation which gave chills in about twenty-five per cent. of the cases injected. We filtered this and while perfectly clear it gave no chills, so we thought that by chance we had come upon the explanation. The next slightly turbid preparation we treated the same way, but without preventing the chills. What was more peculiar was that the good preparation was mixed serum from horses A and B, and the poor preparation was from horse B only. We now have a preparation which has become hazy and yet produces no chills, so that we see there is an unknown factor in the serum as well as in the patient, and that substances in one serum may

inhibit the action of those in another. I believe there must be a difference between what causes a delayed and an immediate reaction.

MRS. PARKER: In regard to Dr. Cooke's observation that he and Dr. Coca were not able to prove that pollen is antigenic, I wish to say that I have been able to show that alkaline extracts of ragweed pollen have definite antigenic properties as shown by the Dale method. At the present time I am sensitizing a series of guinea pigs in order to determine whether they can be made generally anaphylactic to pollen. Since the Dale method is the more delicate test and since it proves that pollen is antigenic I thought it worth while to report the fact that I have obtained positive results with this method.

DR. BERGER: Is it possible by means of the skin test to tell whether a patient is partially or to a marked degree desensitized after treatment with pollen extract or any antigen? Dr. Schloss reported a series of cases last June in which he fed egg-white to infants. If the patient developed urticaria following the ingestion of egg-white he noticed that while the urticaria was present the skin test was negative or reduced. He reported several cases where the skin reaction was markedly reduced during an attack of asthma. Is the skin sensitive to bacteria? If the patient has accompanying his asthma a bacterial infection of the chest would the skin be an index of sensitiveness to the bacteria? I would like to know if the various bacterial extracts which are on the market are of any value. The difficulty I have found with the intradermal method is to get an extract of horse dander or cat hair into solution. You can obtain a dehydrated product which comes in solid form and which has to be diluted with sodium hydroxide and subsequently neutralized with acid. I wonder whether that product is the one Dr. Cooke used, or did he use a suspension of the dander in saline or water.

DR. MACKENZIE: In regard to the question raised by Dr. Huntoon, I evidently did not make myself clear that at the time the serum was administered to these patients only one was hypersensitive to horse serum. All the others were normal people with negative skin reactions. Last year before this Society I showed the curves of antigen and antibody in the circulation for the individual who was hypersensitive at the time serum was administered. He showed immediate and accelerated reactions. In him the antibody production was also earlier. He had not only an accelerated symptomatic reaction, but an accelerated antibody formation. All the other individuals in this series were not hypersensitive to horse serum at the time it was first administered. The susceptibility refers to the susceptibility to serum disease.

As to the error in technique, I did not wish to take up much time in the paper to speak of it. In one individual there was a severe serum reaction and a high titer of precipitin. If he had conformed with the other members of the series, the precipitinogen should have disappeared with the rise of the precipitin to a high titer, but it did not. That patient was studied before we realized the importance of testing the anti-horse serum for traces of antigen, and it was possible that the patient's serum containing an abundance of antibody was precipitating traces of antigen in the anti-horse rabbit serum we were using.

As to the differences in sera which Dr. Park spoke of, I cannot say anything with accuracy on that, because I have not tabulated the cases according to what serum was used in any particular individual, but we have used only serum from the Rockefeller Institute and from the Department of Health. I am not sure just how many cases in the series were treated with one or the other serum.

DR. COOKE: In reference to Dr. MacKenzie's paper, I would like to say that if he can throw any light on the question of serum disease it is going to be a great help in the study of these delayed clinical reactions we see to-day.

I am also interested to know from Mrs. Parker that she has been able to demonstrate the antigenic properties of the pollen extract. Experiments of Coca, Flood and myself two years ago failed to show any antibody formation to ragweed pollen extract by the usual guinea-pig experiment.

There were a few questions as regards desensitization. When one injects hay fever patients with pollen extracts there is a decrease in the sensitiveness of the mucous membrane, but very little difference in the intradermal reaction. If there is any difference in the cutaneous reaction at all there is a tendency to disappearance of the itching which is usually a very marked manifestation of the reaction.

In the case of allergic children one has to be very careful in making any statement that what is being done in the way of injection or feeding has any effect on the course of the disease, because there is a tendency in all children to lose, naturally, the hypersensitive reaction to foods when this hypersensitiveness existed early in life, for in such cases it usually disappears from the eighth to the tenth year, at which time, although cutaneous reactions may or may not be present, the clinical reaction on the ingestion of the particular food has entirely disappeared. This is not due to any treatment. It is not due to injections or to feeding, because most of these children lose their hypersensitiveness when the specific food has never been eaten or injected. It is a natural phenomenon.

With regard to the bacterial proteins and sensitization, it is very difficult to say much. So far, using solutions of various bacterial proteins, we have never yet been able to get an immediate marked positive reaction that looked at all like the immediate reactions one gets with foods and pollen extracts, and furthermore, such reactions as do occur do not correspond to the bacteria that are isolated from the bronchial tract or from the nasopharynx. The whole question of bacterial hypersensitiveness is one about which we know very little at the present time.

There was one other question about the preparation of the extracts we used. One must always bear in mind that these reactions of necessity take place from some readily absorbable substance. It must be dissolved in the tears, or in the saliva, and be readily absorbable in order to get into contact with the cells. This being so, it is perfectly evident that when one speaks of getting reactions to cat hair or dog hair it is absolutely a misconception. What you do get reactions to are the epithelial cells that are attached, and the hair has nothing to do with the reaction at all. Solutions

of dander of animals are readily obtained, and there is no trouble at all about dealing with an insoluble substance.

# DIFFUSE ENDOTHELIOMA OF BONE

JAMES EWING, M.D.

For some years I have been encountering in material curetted from bone tumors a structure which differed markedly from that of osteogenic sarcoma, was not identical with any known form of myeloma, and which had to be designated by the vague term "round cell sarcoma" of unknown origin and nature. I had no opportunity of following the course or learning the outcome of these cases, as most of them were treated by amputation of the limb.

Recently a case came under observation at the Memorial Hospital which revealed that this tumor is highly susceptible to radium, a fact that convinced me that the disease was entirely different from osteogenic sarcoma, which resists treatment by the physical agents.

The story of this case is briefly as follows:

A fourteen-year-old girl had been treated by an outside physician in 1918 for nasal discharge and occasional bleeding. Some ocular symptoms led to the suggestion of congenital lues, and a Wassermann reaction being weakly positive, salvarsan was administered. In November, 1918, while pulling on a rope, a spontaneous fracture of the ulna occurred, followed by swelling which gradually subsided. In January, 1919, the swelling recurred and continued with pain and disability until a well-marked tumor occupied the upper part of the arm. This tumor was noted to fluctuate in size. The veins of the skin were dilated, and the appearance led to the diagnosis of osteogenic sarcoma. Eight injections of Coley's toxins were administered at Mount Sinai Hospital, without notable effect.

On April twelfth at the Memorial Hospital a radium pack of 12,760 millicurie hours was applied to the arm, and followed by two other packs at intervals of two weeks. The tumor began to recede at once and at the end of five weeks no external swelling remained.

On admission the radiograph showed a peculiar diffuse fading of the upper half of the shaft of the radius, and a faint line from the old fracture. The outline of the slightly swollen shaft was smooth (Fig. 1); there was no

bone formation, no point of perforation, or area of erosion of the shaft, all of which features told against osteogenic sarcoma. The prompt recession

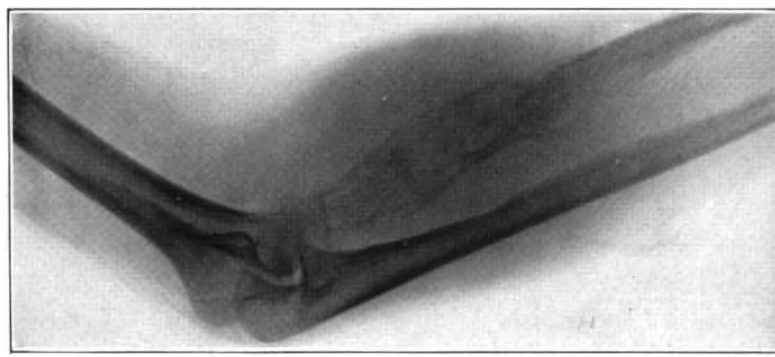


FIG. 1. Diffuse endothelioma of radius. Diffuse absorption of shaft; spontaneous fracture; invasion of soft parts.

under radium was also quite unlike our experience with osteogenic sarcoma (Fig. 2). With the recession of the tumor the shaft was well restored and normal function regained. The patient left the hospital with instructions to return weekly for observation, which was continued for several months.

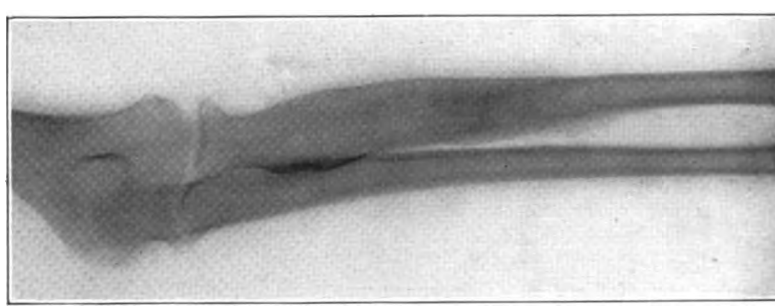


FIG. 2. Diffuse endothelioma of radius. After radium treatment.

The patient then came under the care of her original physician who noted persistence of the nasal and ocular symptoms, and, regarding the tumor of the radius as luetic, he instituted vigorous treatment by salvarsan. The injections, however, were followed by severe toxic symptoms, vomiting, bloody urine, collapse, and progressive anemia. Later injections of cacodylate of sodium were administered for the anemia. The patient failed steadily and the tumor of the arm began to reappear. There was now an

irregular fever up to 103° F. The urine failed to show Bence-Jones protein.

In October, 1920, the patient returned to the Memorial Hospital with a definite recurrence of the tumor, and owing to the conflict of opinion, a portion of tissue was removed for diagnosis. It proved to be a round cell growth of the above-mentioned type. Other tumors had now appeared plainly in the skull. There was exophthalmos. The eye grounds showed choked disc and nerve atrophy. The radiograph of the lungs was negative. Anemia and cachexia progressed rapidly, and death occurred on December 23, 1920. The total duration was about thirty months.

During the past four months I have seen six other cases of this disease. They occurred in subjects from fourteen to nineteen years of age. The bones affected were tibia, ulna, ischium, parietal and scapula. The tumors grew rather slowly, requiring some months to attract attention, but they were accompanied by attacks of pain and disability. One boy complained only of intermittent attacks of pain after exercise during the summer, but in November a smooth swelling appeared over the upper half of the leg. Several tumors were found to fluctuate in size, a symptom due to their vascularity. All were rather painful and tender.

The radiographs give characteristic features on which a diagnosis may be based with considerable certainty. A large portion or the whole of the shaft is involved, but the ends are generally spared, contrary to the rule with osteogenic sarcoma. The shaft is slightly widened, but the main alteration is a gradual diffuse fading of the bone structure. Bone production has been entirely absent. Some of the bones appeared honeycombed. Perforation of the shaft and sharp limitation of the process are wanting. The central excavation with widened bony capsule, as seen in benign giant cell tumors, is missing. The radiograph is therefore rather specific.

Under radium treatment the tumor recedes and the shaft gradually becomes well defined with little deformity and no eccentric bone formation.

In seven cases the tissue was examined microscopically, and in all the structure was nearly identical. The growth was composed of broad sheets of small polyhedral cells with pale cytoplasm, small hyperchromatic nuclei, well-defined cell borders, and

complete absence of intercellular material. Hydropic degeneration often affects large islands of cells, in which only nuclei and cell borders are visible. Necrosis occurred after radium applications. There is very little desmoplastic quality, but the tumor cells readily infiltrate muscle and pass along the fasciæ. In none were pulmonary or other forms of metastases observed. In the case cited the tumors of the skull were regarded as primary and of long standing. In some sections the cells were of increased size, while in others they were smaller and more compact, and approached the morphology of plasma cells. However, no definite areas of plasma cells have been seen in any case.

The probable endothelial nature of the tumor was suggested by the form of the cells, and especially by the appearance in broad

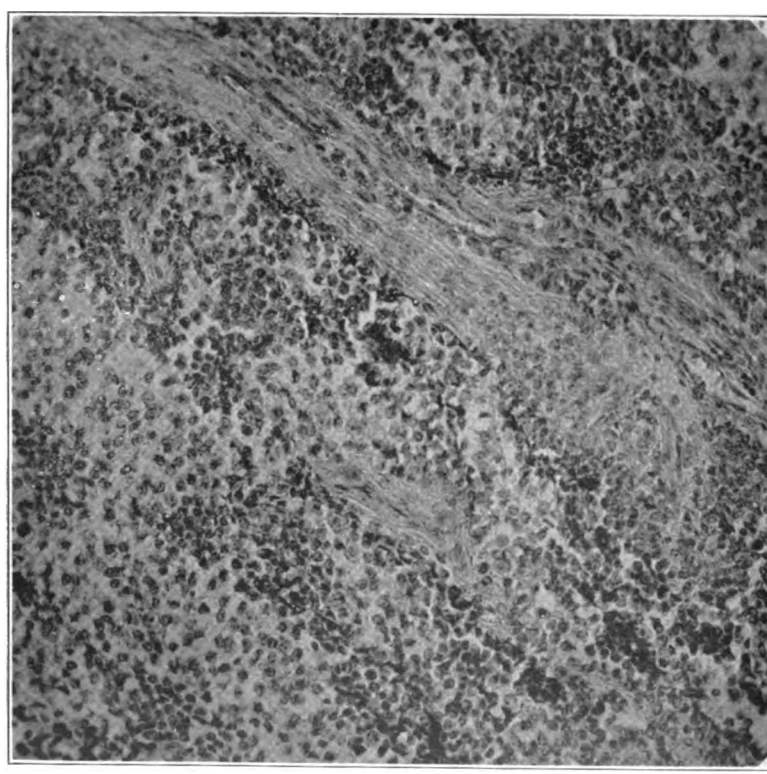


FIG. 3. Diffuse endothelioma of bone. Compact structure of large polyhedral cells.

sheets of polyhedral cells without intervening stroma (Fig. 3). This origin, however, did not seem to be fully supported until I encountered sections in one case in which the cells were found to line a complex series of fine channels inclosing intact blood (Fig.

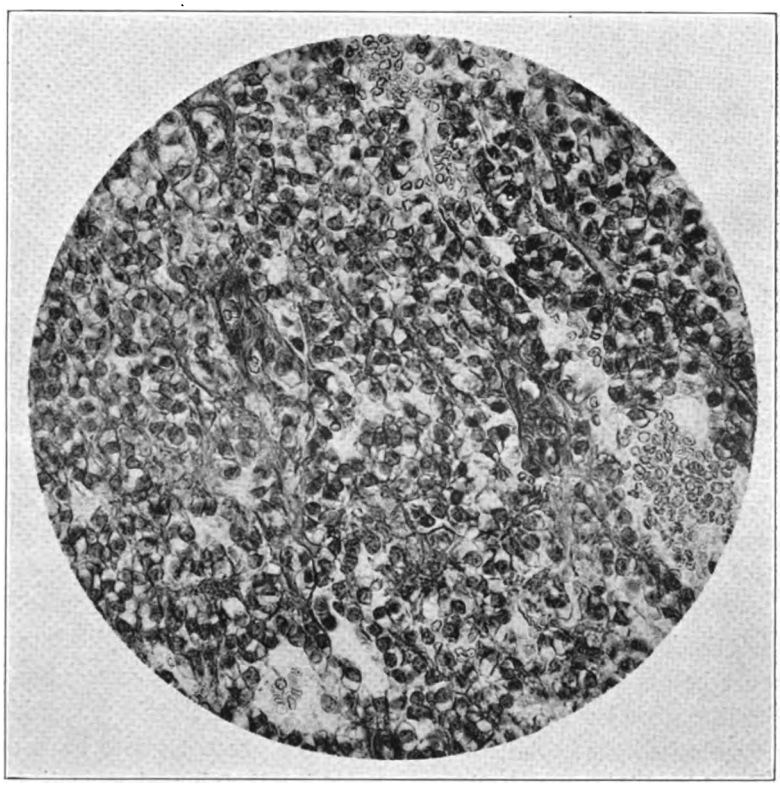


FIG. 4. Diffuse endothelioma of bone. Showing blood sinuses lined by tumor cells.

4). Here the endothelial character of the cells was quite pronounced, but they were much smaller than those occurring in angio-endothelioma, with which this tumor is doubtless closely related. In other portions of the same growth the cells appeared in diffuse sheets without capillary lumina, as seen in the other tumors of the series.

The exact point of origin of the growth is not clear, but the

early rarefaction of the bone indicates that the disease begins in the blood vessels of the bone tissue. Yet an involvement, simultaneous or early, of the vessels of the bone marrow can not be excluded. In the discussions of multiple endothelioma in the literature some authors thought they could trace the origin to the vessels, blood or lymph, of the periosteum. Many multiple endotheliomas, as in Marckwald's case, have appeared well within the bone marrow.

The designation of the tumor as endothelioma rather than as myeloma seems advisable, since myeloma is properly reserved for tumors derived from the specific cells of bone marrow.

The possible relation of the endothelial tumor to plasma cell or other forms of multiple myeloma deserves consideration, but the evidence at present available indicates that the two processes are distinct. I have found no definite plasma cells in any of the specimens. Plasma-cell myeloma is nearly always multiple and often very widespread. Bence-Jones protein has not appeared in any of the cases of endothelioma, but is often absent in myeloma. Multiple myeloma also perforates the bone rapidly and destroys it completely, while these tumors cause slow, rather diffuse rarefaction.

A relation to the angio-endotheliomas and other forms of endothelioma, solitary and multiple, described in the literature, must be assumed to exist. Most of these tumors accessible in the literature have occurred in adults and were clearly recognized as endothelioma. All the tumors of the present series have occurred in children, and with one exception they have been solitary.

The main point of the present communication lies in the demonstration that there is a rather common tumor occurring in young subjects, commonly identified with osteogenic sarcoma, and usually called round cell sarcoma, which is really of endothelial origin, and which is marked by such peculiar gross anatomical, clincal, and therapeutic features as to constitute a specific neoplastic disease of bone.

*Discussion:*

DR. LARKIN: Dr. Ewing's contribution was such an illuminating one that I think a discussion of the study he has made of bone tumors for many years would be hardly possible in a short time. The idea which he has tried to give us of the endothelial origin of this class of tumors which we have been wont to regard as sarcomas for many years seems to be most convincing. If you look back at some of the cases which have been reported by a number of observers, I think that Dr. Ewing's ideas meet with the more radical views which we have of the conception of tumors. I believe that when you commence to look over a great many of your tumors which for many years have been classed as sarcomas that the more recent view of classifying them according to the genesis of the type of cells from which they spring will force us to accept Dr. Ewing's idea of the origin of this particular class of tumors. Not long ago Dr. Ewing reported a number of tumors in lymph nodes of endothelial origin. It was a notable contribution to pathological science, and I think that his views as expressed to-night represent the more modern view, so that we will have to look over and classify a good many of our bone tumors belonging in the class of angioendothelioma.

DR. MOSCHCOWITZ: I would like to ask whether any oxidase stains were made on the sections, and I would like to know whether any metaplastic bone formation was noticed. It seemed to me in one of the lantern slides there were distinct shadows of new bone formation. This would perhaps make us skeptical in regard to accepting the endothelial interpretation.

DR. SYMMERS: I should like to ask if there was any possibility of these individuals suffering from primary tumors of the kidney, notably the so-called hypernephromas, which often metastasize to bone, and the histology of which is not unlike that of the preparation thrown on the screen.

DR. EWING: I do not believe that any of the modern methods of determining biological differences of tumor cells were used. I do not consider them reliable differential signs and there are contributions in the recent literature which point out the uncertainty of these reactions in myeloma. Perhaps Dr. Martland will come to my help and tell you about his work on one of the cases.

In regard to metaplastic bone formation, if there were such metaplastic bone formation I think we should have to abandon our idea of an endothelial origin. That is one of the things the tumor does not show, and while this might be indicated as a possibility it certainly cannot be proven by X-ray plates, but only by microscopical study, and that study indicates the absence of such bone formation. In the gross specimen exhibited there are trabeculæ of bone at some distance from their original position which I think can be explained as mechanical displacements resulting from the growth of the tumor. The microscope shows that these trabeculæ are dissolving bone and not forming bone. The point which our President raises in regard to a primary tumor elsewhere has been the main question in the minds of those who are inclined to recognize endotheliomas in bone. I

think in the angio-endotheliomas which are very destructive and which contain large blood vessels filled with blood, the cells do look like the large clear cells of the papillary carcinoma of the kidney, but in this tumor we have an entirely different type of cell, which I think Dr. Symmers would recognize as different from those of any tumor of the adrenal or kidney.

Another point is that these tumors occurred in young subjects, and there were no signs of malignant tumors elsewhere. One of the patients lived for two years. Renal tumors do not occur in young subjects of this type. I won't say they never occur, but that is not the age incidence of metastasizing clear-cell carcinoma of the kidney. It occurs in adults or older people. The age incidence is not so much against the origin of the angio-endotheliomas from renal tumors; angio-endotheliomas occur in adults. I would not offer a diagnosis of angio-endothelioma of bone in an adult without great care. Diffuse endotheliomas of children are different. I do not think the same suspicions surround them of possible metastatic origin that exist with the others.

DR. MARTLAND: Dr. Ewing's last case was a boy about seventeen years of age with a tumor on the parietal bone of two months' duration. We thought he might have multiple myeloma (Kahler's disease). Sections were stained for oxidase granules and were negative. He was examined very carefully for evidence of a primary growth elsewhere, especially to rule out hypernephroma or kidney tumor, and his skeleton was X-rayed for other growths with negative results.

I think Dr. Ewing has offered a distinct contribution to the pathology, diagnosis and treatment of malignant primary disease of bone, in calling attention to this type of lesion, because it has undoubtedly been diagnosed by most pathologists as osteogenic sarcoma.

Dr. Ewing states that these tumors are possibly amenable to radium treatment. In osteogenic sarcoma, especially the periosteal variety, amputation and resection have offered little hope (Bloodgood's series showing less than 4 per cent. of cures).

The treatment of malignant bone tumors is therefore so hopeless that it seems to me before any mutilating amputation or resection is performed an absolutely accurate diagnosis should be made. Such a diagnosis can in many instances be made from the X-ray in conjunction with the situation, age of patient, etc. But most cases, I believe, will require an exploratory operation to obtain an accurate diagnosis. The exploratory operation must be done under proper technique to prevent spreading of tumor, especially myxomatous tissue (cauterization with carbolic or actual cautery). If all means fail to make a diagnosis of malignancy, the tumor should be treated as a benign one.

# CHEMICAL CHANGES IN THE BLOOD IN NEPHRITIS

VICTOR C. MYERS, PH.D.

*(From the Laboratory of Pathological Chemistry, New York Post-Graduate Medical School and Hospital)*

As is well known, the blood acts as the common carrier of food products to the tissues, and of waste products to the organs of excretion, and further aids in maintaining the neutrality of the body tissues and the normal osmotic relations. Oxygen, for example, is carried from the lungs to the tissues by the blood, while carbon dioxide is returned to the lungs for excretion by the same medium. Likewise the food nitrogen in the form of amino acids is transported by the blood to the various tissues, while the nitrogenous waste products, such as urea, uric acid and creatinine, are carried to the kidneys for excretion. The kidneys normally eliminate the end products of nitrogenous metabolism quickly and quite completely, so that in health they are never present in the blood in high concentration, but with impairment in renal function these substances may accumulate.

Normally the neutrality of the blood is maintained in considerable part by the blood bicarbonate. In acidosis, whether it be caused by the formation of $\beta$-hydroxybutyric acid as in diabetes or the non-elimination of acid phosphate as in nephritis, these acid substances combine with the bicarbonate, robbing the body of its alkali reserve, and thus lowering the $CO_2$ combining power of the blood.

The maintenance of the normal osmotic relations of the blood would appear to depend in large part upon the blood chlorides. In the so-called parenchymatous nephritis the ability to excrete the chlorides is impaired. To preserve the normal osmotic relations of the body fluids water is retained and edema results.

Usually the sugar of the blood is maintained at the very constant level of about 0.1 per cent., presumably through the glycogenic function of the liver, but in conditions of defective glycogen

storage, with or without defective glucose oxidation, we have an increase in the blood sugar. When this exceeds the threshold level of about 0.15 to 0.18 per cent., the protective mechanism of the kidney allows the excess of sugar to escape into the urine. In so-called renal diabetes, however, this threshold is lowered, while in advanced diabetes, with renal complications, it is frequently raised. Nephritis is quite generally accompanied by a mild hyperglycemia.

From the foregoing it is apparent that kidney disease may result in a change in the blood content of such constituents as uric acid, urea, creatinine, $CO_2$, chlorides and sugar, in addition to many others. It should be borne in mind that the clinical symptoms of nephritis are the result of the pathological condition of the kidneys only indirectly, but rather the result of the accumulation of various products in the blood and tissues due to deficient kidney function.

How may blood analyses be used practically as an aid in the diagnosis, prognosis and treatment of renal disease? The function of the kidneys is to eliminate nitrogenous and other waste products from the body; consequently, a diagnosis based on the impairment in kidney function is especially useful, since it points the way to an intelligent treatment. The routine urine tests of specific gravity, protein, casts and blood cells are of considerable value in indicating the presence or absence of renal disease, but they furnish little information regarding renal function. It is for this reason that the blood tests are particularly useful, since they enable us to gauge the severity of the condition and formulate an opinion regarding the probable outcome. For example, a case may show a moderate amount of protein in the urine with a perfectly normal blood urea, and thus have a favorable prognosis, while another case may give a trace or even a negative test for protein, but have a high blood creatinine, indicating that a fatal outcome is a matter of only a few weeks or months. In the treatment of nephritis it will be conceded, I think, that dietary restriction in nitrogen or chlorides can be made intelligently only when a knowledge of the degree of impairment in the function of eliminating the nitrogen or chlorides is at hand.

There would appear to be little doubt that cases of incipient nephritis are accompanied by an appreciable rise in the blood uric acid, although a rise in the blood urea can probably be taken as a safer sign of impaired kidney function. It is certainly true that the urea nitrogen falls within very narrow limits for perfectly normal individuals. As soon as one passes to hospital patients, however, figures above 15 mg. of urea nitrogen are found. Figures over 20 on the usual restricted diet of the hospital would suggest impaired kidney function. Creatinine appears to be more readily eliminated than either uric acid or urea, and it is not, as a rule, until the blood urea has doubled, or more than doubled the normal, that there is a very appreciable increase in this purely endogenous waste product derived apparently from muscle metabolism. The normal for the creatinine of the blood is approximately 1 to 2 mg. per 100 c.c., and figures over 3.5 mg. can be viewed with grave concern, while over 5 mg. are almost invariably indications of an early fatal termination. The only possible exceptions are cases where the retention is due to some acute renal condition, such as acute nephritis and mild bichloride poisoning.

Normally the $CO_2$ combining power of the blood plasma of the adult amounts to 55 to 75 c.c. per 100. In moderate acidosis figures between 30 and 40 are observed, while in severe acidosis the figures are below 30. All advanced cases of chronic nephritis suffer from acidosis, and in some cases this is apparently the cause of death. It may also be noted that cases of acute nephritis occasionally show marked acidosis.

In parenchymatous nephritis, if we may be allowed to use this term, the findings are quite different. Here the nitrogen retention is comparatively small, although the examination of the blood generally discloses a retention of chlorides. The figures for urea nitrogen seldom exceed 30 mg., except in the terminal stages of the disease, and generally fall between this figure and 15. The figures for chlorides, expressed as sodium chloride, frequently exceed 0.6 per cent. for whole blood and 0.7 per cent. for plasma.

It is of interest to note that many advanced cases of malignancy, possibly as a result of the toxemia, give the chemical blood picture of moderately severe nephritis; also that many cases of pneumonia show definite evidence of nitrogen retention; while in the terminal stages of the disease a severe acidosis quite generally develops, apparently as an indirect result of the marked arterial oxygen unsaturation of the blood.

Relatively high figures for the nitrogenous waste products are frequently noted in intestinal obstruction and lead poisoning, while a slight retention is often observed in gastric and duodenal ulcer, possibly for the same reason that retention is found in intestinal obstruction. The moderate nitrogen retention sometimes encountered in syphilis and certain cardiac conditions is apparently due to renal complications.

Since the blood findings in eclampsia are to be considered by Dr. Killian in the next paper, they will not be discussed here.

Kidney disorders, according to ordinary clinical groupings, give the following chemical blood pictures:

1. *Incipient nephritis:* Slight nitrogen retention (high uric acid, slightly elevated urea).

2. *Advanced chronic nephritis:* Marked nitrogen retention (including high creatinine), with or without severe acidosis.

3. *Acute nephritis:* (*a*) Mild,—moderate nitrogen retention; (*b*) severe,—moderate or marked nitrogen retention, with or without acidosis.

4. *Parenchymatous nephritis:* Slight or only moderate nitrogen retention, generally definite salt retention, occasionally marked hypercholesterolemia.

Although a diagnosis can best be made in connection with the full clinical history of the case, the findings of groups 2 and 4 are so typical as to allow in most instances of a diagnosis on the basis of the blood analysis alone. The terms employed above have been used solely with the idea of giving the different groups a simple name and without any anatomical significance.

A few illustrative cases which fall into the above groups are tabulated below:

| Group | Uric Acid | Urea N | Creatinine | $CO_2$ Combining Power c.c. to 100 | Chlorides as NaCl Per Cent. |
|---|---|---|---|---|---|
| | Mg. to 100 c.c. of Blood | | | | |
| 1..... | 9.5 | 25 | 2.5 | | |
| 2..... | 7.7 | 200 | 26.7 | 12 | |
| 2..... | — | 147 | 5.7 | 40 | 0.50 |
| 3..... | — | 50 | 2.5 | 50 | |
| 3..... | 11.2 | 93 | 5.9 | 54 | |
| 3..... | 9.5 | 44 | 3.5 | 22 | |
| 4..... | 2.3 | 28 | 1.9 | 56 | 0.70 |
| 4..... | 4.5 | 22 | 2.1 | | Increased |

Normal figures for the uric acid of the blood may be given as 2 to 3 mg. per 100 c.c., urea N 12 to 15 mg., creatinine 1 to 2 mg., $CO_2$ combining power 55 to 75 c.c. per 100 of plasma, and chloride of whole blood 0.45 to 0.50 per cent.

# SIGNIFICANT CHEMICAL CHANGES IN THE BLOOD IN THE TOXEMIAS OF PREGNANCY

JOHN A. KILLIAN, PH.D.

*(From the Laboratory of Pathological Chemistry, New York Post Graduate Medical School and Hospital, and the Department of Chemistry, Fordham University, N. Y.)*

The first step in the study of the chemical changes involved in the toxemias of pregnancy was to determine whether in fairly comprehensive analyses of the blood a large group of representative toxic pregnant cases manifest any characteristic variations when compared with normal pregnant cases. The results obtained in this first step of the investigation are presented below, and, we believe, they admit of the deduction of definite conclusions.

At the outset it was evident that the toxic cases might be conveniently divided into three distinct groups:

1. Nephritic toxemias—including a group of cases that in their previous histories gave evidence of a preexisting nephritis which was not consequent to the pregnancy, but rather was aggravated by it.

2. Hepatic toxemias or true eclampsias—comprising cases that gave no evidence of preexisting impairment of renal function. By the clinical symptoms alone these cases can be readily differentiated from those of the former group.
3. Mixed toxemias—the cases within this group present evidence of a mild impairment of renal function which, however, resulted from the hepatic toxemias. The clinical findings alone are not sufficient to differentiate this group from group 2.

Four cases, carefully selected as normal pregnancies, showed low normal or slightly decreased figures for nonprotein nitrogen, with proportionately decreased urea nitrogen. The urea nitrogen formed from 45 to 50 per cent. of the nonprotein nitrogen. Uric acid, creatinine, chlorides and sugar proved to be normal, but the carbon dioxide combining power was slightly lowered. No hypertension was observed. The urine, on the other hand, from time to time contained traces of protein.

Four patients, all multiparæ, suffering from nephritic toxemias, were studied. Of these cases three showed impaired nitrogen excretion, whereas the fourth was a case of parenchymatous nephritis, with chloride retention. In the first three cases the nonprotein nitrogen was increased from 45 to 106 mg., the urea nitrogen in a similar manner was elevated from 28 to 72 mg., forming from 62 to 67 per cent. of the nonprotein nitrogen. The uric acid figures ranged from 4.8 to 8.1 mg., but the creatinine was only slightly increased. The fourth case showed no evidence of nitrogen retention, but the chloride concentration was considerably increased (0.52 per cent.) and was found to be associated with a marked edema. The decrease in the carbon dioxide combining power was not greater than in the normal cases. Large amounts of protein and occasionally casts were found in the urine. Further, these cases were characterized by a pronounced hypertension, and albuminuric retinitis with marked disturbance of visual acuity. Following the removal of the fœtus from the uterus, there was at most only a slight general improvement, with

practically no return to normal in the chemical composition of the blood.

Twelve cases of hepatic toxemias or true eclampsias came under our observation, including two cases of pernicious vomiting and two cases of post-partum eclampsia. All of these cases were primiparæ save three, but the previous pregnancies of these three had also been toxic. In all instances a rise in the nonprotein nitrogen (34 to 56 mg.) was found; the urea nitrogen, on the contrary, was definitely decreased, constituting from 15 to 34 per cent. of the nonprotein nitrogen. The increase in the uric acid (3.5 to 11.0 mg.) was very striking. The greatest disproportion of urea nitrogen to the nonprotein nitrogen, the highest uric acid figures and the largest output of protein in the urine were found in the most toxic cases. This observed increase in uric acid, we believe, may be attributed to a renal irritation resulting from the toxemia, producing a slight impairment of kidney function.

No disturbance of the creatinine concentration of the blood was noted, but in the majority of cases there was a mild hyperglycemia and a pronounced decrease in the carbon dioxide combining power of the blood. In fact, two cases died of postoperative acidosis. A normal chloride concentration of the blood was found to be the rule, except in a few cases where high chloride figures were encountered in edematous patients. The protein excretion varied from a trace to a large amount. Although all cases had increased blood pressures, this elevation was not as pronounced as in the nephritic toxemias. Furthermore, unlike the nephritic toxemias, the cases in this group manifested a prompt improvement as judged by the chemical composition of the blood and as well by the clinical signs, following the removal of the fœtus from the uterus. Finally, no pathological changes were noted in the examination of the eye-grounds.

The mixed toxemias, apparently, represent a more severe degree of toxicity than the hepatic toxemias. The toxic factors in both groups of cases, no doubt, are identical, but in the latter it has produced a more severe impairment of renal function, result-

ing not only in the retention of uric acid, but likewise in a moderate accumulation of urea nitrogen. The nonprotein nitrogen was found to be from 56 to 64 mg., and although the urea nitrogen was considerably increased, nevertheless it formed but a small portion of the nonprotein nitrogen (32 to 38 per cent.). In this particular these cases differ from both the nephritic and hepatic toxemias; in other respects, however, they gave findings similar to the hepatic toxemias.

Dr. I. J. Levy read a paper on "The Relation of the Histopathology of the Kidney to Blood Nitrogen," which will appear in full elsewhere.

*Discussion:*

DR. MOSCHCOWITZ: Dr. Levy's presentation interested me enormously. I wish I possessed Dr. Levy's confidence in trying to partition out the various types of nephritis as he has done. For years I have been attempting to correlate function and anatomy in disease of the kidney and have been unable to predict the "type" of nephritis that will be found at autopsy from functional tests alone. It seems to me that such a prediction will resolve itself largely into a matter of guesswork. There are various reasons for this. The most important is the fact that in the past we have been regarding the "type" of nephritis as an end product. It seems to me rather that these "types" are not pure in the biological sense, but run into each other, and thay they represent stages in a fairly well-defined pathogenesis beginning in an early glomerulo-nephritis and ending in the familiar contracted kidney. I refer now, of course, only to those kidneys that may be comprised under the term arterio-capillary fibrosis. The parenchymatous, the kidneys of subacute bacterial endocarditis, and the amyloid do not enter into this discussion. I propose to report shortly upon six autopsies in which marked evidences of nephritis were present during life, although at post-mortem the kidneys showed barely perceptible damage. On the other hand, all pathologists are familiar with the phenomenon of finding profoundly contracted kidneys at post-mortem although during life there were no evidences of nephritis. These patients died of something else. The point I wish to make clear is that clinical and anatomical nephritis are two entirely different things and can only be correlated in a very broad sense.

I have submitted in a number of papers the thesis that arterio-capillary fibrosis is a primary vascular disease. Whether the initial change is in the glomeruli or the terminal arterioles is not a matter of great consequence, although I believe it is in the former. All the changes that occur in such a kidney can be explained genetically from the progression of such early lesions. As Dr. Levy pointed out, the vast majority of patients with "nephritis" die a cardiac and not a renal death. They die of decompensation of the cardio-vascular apparatus just as patients do who have frank valvular

disease. This is one of the reasons why it is so hard to interpret blood figures, such as Dr. Levy and Dr. Myers have presented, in terms of anatomy. Their greatest value, as Dr. Myers pointed out, is in estimating prognosis. The trouble with these figures in attempting an estimate of renal function is that they are dependent on too many extra-renal factors of which the most important are diet, water intake, the function of other viscera, the liver for instance, and myocardial insufficiency. The latter, in my opinion, is the most important factor. Non-nitrogenous retention seems to be proportional more directly to myocardiac insufficiency than to any other factor. I can confirm the findings of Rowntree and Geraghty, who showed both clinically and experimentally that tests for renal function depended largely upon the amount of chronic congestion of the viscera, a condition practically always present clinically and anatomically in nephritis. It is for this reason that a method of determining the volume output of the heart would be most desirable; unfortunately our instruments of precision afford no guide for the determination of this highly important function.

DR. SCHWARZ: I should like to say a few words from the clinical standpoint, that we endeavor to get some of the types straight in our minds. I do not think we should look at this quite as darkly as Dr. Moschcowitz does, for observing these cases at the bedside there are certain distinct groups which are diagnosticated by the chemical examination of the blood. In the first group we find blood in the urine without an increased blood pressure, some reduction in the amount of urine excreted and some retention of the nitrogenous substances in the blood. These cases have an etiological factor—either scarlet fever or naso-pharyngeal conditions. These may or may not clear up and become chronic. The second group without any etiological factor but sometimes, however, due to diphtheria, has edema which is more or less persistent, no increased blood pressure, no retention of nitrogenous substances in the blood but a marked increased cholesterol in the blood. The third type not seen so frequently in children, but more often in adults, is always associated with hypertension and changes in the eyeground indicative of albuminuria retinitis, marked polyuria, polydypsia and low specific gravity, and is associated with scerotic changes in the kidney and no change in the blood chemistry.

## LIPOMA OF THE UTERUS

ROBERT C. SCHLEUSSNER, M.D.

*(From the Pathological Laboratory of the Lenox Hill Hospital, New York City)*

In view of the infrequent occurrence of lipomata of the uterus, it was thought on encountering this case that it would be of interest to report it. Including the case here reported, there

are but seventeen such tumors on record. Ellis quotes statistics of Williams, who found no case among 2,649 uterine tumors collected from four large London hospitals, and statistics of Gurlt, who encountered no case among 4,115 uterine tumors on record in the Vienna hospitals. In a review of the Index Medicus from 1890 through 1919 I found no case reported from New York City. This is the first case to occur among 14,500 operative specimens of all types examined at the Lenox Hill Hospital.

Of the seventeen cases on record, ten were collected from the literature by Seydel, who added a case of his own, in 1903. Pollack reported an additional case in 1903. Elkins and Haythorn in 1917 reported a case and enumerated the three cases reported in the interval between 1903 and 1917 by Ellis (1907), Sitzenfrey (1910), and Ley (1914).

The various case reports, with their comments, which were written from time to time as the tumors were encountered, cover quite comprehensively all that is known of the condition. This is particularly true of the paper written by Seydel, around whose paper the literature may be said to center. He reviewed critically all the literature to date, admitting to his list of cases only such as had been carefully investigated and described and definitely proven to be lipomata or lipomyomata. Knox in 1901 was the first one in recent years in this country to describe a case, though Schoinski in 1880 described a case which was accepted by Seydel.

Clinically there is nothing to distinguish these tumors from other non-malignant tumors of the uterus. It may be noted that the patients were for the most part from fifty to sixty years of age, though one patient with a cervical polypoid lipoma was but twenty-eight years old.

The tumors have varied both in their location and in the details of their structure. Four occurred as cervical polyps, the remaining thirteen as tumors of the body of the uterus. Seven, including the one here reported, are listed as simple lipomas. Of these seven tumors, two occurred as cervical polyps. The other ten tumors are classed as lipomyomas. These showed varying quantities of fibrous and smooth muscle tissue in the septa be-

tween the fat alveoli, while one tumor also showed sarcomatous areas. Of the ten lipomyomas two occurred as cervical polyps. The distinction between lipoma and lipomyoma is an arbitrary one and may vary with the viewpoint of the author. In general, it seems that the name lipoma has been applied to those tumors where the fatty tissue seemed to be sharply set off against the surrounding fibromuscular tissue and where no muscle strands entering the fatty tissue from the capsule have been evident. Those tumors, on the other hand, where the fibromuscular tissue has been seen very evidently to enter the fatty tissue from the capsule and disperse among the fat cells have been called myolipoma, or fibromyolipoma. But between the pure lipoma and the tumor, with thick strands of fibromuscular tissue entering the fat zone, there are all gradations. Thus in the tumor I shall describe the fibromuscular elements separating the alveoli of fat cells are barely to be distinguished at the periphery of the tumor. Taking the viewpoint that these fibromuscular strands are remnants of uterine tissue in the process of being pushed aside by the growing fat cells, I have classed the tumor as a simple lipoma. Perhaps it would be better to follow the lead of Elkins and Haythorn and refer to this entire group of tumors simply as "fatty tumors of the uterus."

Of the histogenesis of the fat cells occurring in these tumors nothing is known. The theories advanced are:

I. That they result from a fatty degeneration of the fibrous or muscular tissue in fibromyoma of the uterus. In support of this theory it has been urged that fatty degeneration has been observed in the muscle cells and connective tissue of these "fatty" tumors, and one author believed that he could trace the process in its various stages from beginning fatty degeneration to completed fat cell. This idea is contrary to present ideas of the specificity of tissue growth. Moreover, some of the tumors have shown no fatty degeneration whatsoever in their connective or muscular tissue.

II. That the fat cells arise by multiplication of fat cells congenitally misplaced.

III. That the fat cells arise by multiplication of fat cells brought into the uterus along with the blood vessels. Seydel quotes R. Meyer on this point, the latter stating that he has observed fatty tissue accompanying blood vessels into the uterus, though never deeply.

The case reported below occurred on the Gynecological Service of Dr. Oastler at the Lenox Hill Hospital:

The patient was a woman sixty years of age.

*Family History:* No significance.

*Past History:* No significance.

*Menstrual History:* Onset at thirteen years; last period fifteen years ago. No bleeding or discharge since.

*Obstetrical History:* One child thirty-five years ago, with normal delivery. No miscarriages.

*Present Illness:* The only symptom was pain in the left lower quadrant of the abdomen of four weeks' duration.

*Physical Examination:* General examination showed nothing of importance. Pelvic examination revealed a large tumor apparently connected with the uterus.

*Working Diagnosis:* Fibromyoma of the uterus.

*Operation:* A large tumor incorporated with the uterus was found lying in Douglas's pouch and bound to the adjacent viscera by adhesions. The entire mass was easily delivered and a supravaginal hysterectomy done.

The patient made an uneventful recovery.

*Gross examination* of the specimen reveals a tumor incorporated with the remnants of the uterus, and a tube and ovary. The tumor is roughly globular in shape and measures about five inches in diameter. In its growth it has distorted the uterus, so that its original position cannot be made out, but it can be seen that it has involved the body of the uterus and that it occupies an intramural position. On section the tumor has an almost uniform pale yellow color. A delicate connective tissue framework is present, but this forms a very inconspicuous part of the picture. The tumor is for the most part sharply marked off from the remnants of uterine wall which surround it, but in places strands of tissue merging with the uterine wall may be seen to enter the tumor proper and subdivide within it.

*Microscopical examination* shows the tumor made up for the greater part of mature fat cells arranged in bundles of various sizes and separated by strands of connective tissue showing various stages of hyaline degeneration. At the margin of the tumor it can be seen that the fat cells abut directly upon a wall showing connective and smooth muscle tissue. Both muscle and fibrous tissue may be demonstrated as components of the strands described in the gross as merging with the uterine wall and then subdividing as they enter the tumor. The thicker strands of fibromuscular tissue in the tumor and the fibromuscular tissue forming the capsule of

the tumor are seen to contain fat cells in small groups or even isolated. It thus appears that there is no sharp line of demarcation between the fatty tumor and the remnants of uterine musculature present, though to be sure the invasion of the uterine wall by the fat cells is limited to the areas immediately adjacent to the tumor. This lack of sharp demarcation between the fatty tumor and the uterine wall has been described in other cases.

To me the most plausible interpretation of the above microscopic picture is that we are dealing with a lipoma of the uterus which in its growth has pushed aside the fibromuscular tissue, and that this latter tissue has then undergone degeneration. Certainly the fibromuscular tissue present does not suggest growth activity. For these reasons I have classed the tumor as a lipoma, though realizing that such a classification is open to criticism.

In concluding, I wish to thank Dr. Rohdenburg, who called my attention to the tumor and permitted me to report it from the laboratory.

*Literature*

SCHOINSKI: *Chicago Med. Recorder,* 1880, vol. I (cited by Knox).
SEEGAR: *Ztschr. f. Wundartze u. Geburtsh.,* 1853, v, 24 (cited by Knox).
SMITH: *Tr. Path. Soc., London,* 1861, xiii, 148 (cited by Knox).
LOBSTEIN: Sur l'organisation de la matrice. Paris. 1803 (cited by Knox).
MECKEL: Handbuch der Pathologischen Anatomie, vol. ii, 311 (cited by Knox).
KNOX: Lipoma of the Uterus. *Bull. Johns Hopkins Hosp.,* 1901, xii, 318.
BRUNINGS: Ueber Lipomyom des Uterus. *Verhandl. d. deutsch. Gesellsch. f. Gyn.,* 1899, viii, 348 (cited by Seydel).
CHIARI: Lipofibromyom des Uterus, Verein Deutsche Aerzte in Prag. *München. med. Wchnschr.,* 1902, s. 946 (cited by Seydel).
v. FRANQUE: Lipomyofibrom des Uterus. *Verhand. G. G.,* 1901, ix, 491 (cited by Seydel).
v. JACOBSON: Zur Kentniss des Secundaren Veranderungen in der Fibromyomen des Uterus. *Ztschr. f. Heilk.,* Bd. 23, N. S. Bd. 3, *Abth. f. path. Anatomie,* 1902, s. 139, and *Ann. de gynec. et d'obst.,* Paris, 1902, lviii, 259 (cited by Seydel).
LEBERT: Atlas der Anat. pathol., Pl. 16, Fig. II (cited by Seydel).
MERKEL: Ueber lipombildung im Uterus. *Beitz. z. path. Anat. u. z. allg. path.,* 1901, xxix, 507 (cited by Seydel).
ORTH: Lehrbuch der Spec. path. Anatomie, Bd. 2, s. 485 (cited by Seydel).
WILMS: Die Mischgeschwulste, Heft 1 and 2, Leipzig, 1899–1901 (cited by Seydel).
SEYDEL: Lipoma-fibromyomatosum Uteri. *Ztschr. f. Geburtsh. u. Gynäk.,* 1903, L, 274.

WALKOFF: Ueber Liposarkombildung im Uterus. *Festschrift. f. Rindfleisch.*, 1907, pp. 212.
ELLIS: Lipoma of the Uterus. *Surg., Gynec., and Obst.*, 1906, 658.
SITZENFREY: Intramuralis Lipomyosarcom der Vorderen Uterusward. *Ztschr. f. Geburtsh. u. Gynäk.*, 1910, lxvii, 32.
LEY: Lipomatosis of a Fibromyoma of the Corpus Uteri. *Jour. Obst. and Gynec. Brit. Emp.*, 1914, xxv, 42.
ELKIN AND HAYTHORN: Fatty Tumors of the Uterus with a Report of a Case and Notes on Classification. *Surg., Gynec. and Obst.*, 1917, xxv, 72.
POLLACK: *Wien. klin. Wchnschr.*, 1903, 68.

*Discussion:*

DR. WOOD: Small masses of fat are not uncommon in fibromyomata, but the appearance of a large discrete tumor of this type is a very great rarity. It seems to me that the most natural thing to assume is not that the tumors are formed by a degeneration of the muscle tissue, but are independent growths, possibly with a developmental basis.

DR. LARKIN: Seydel's article on this peculiar condition of the uterus is probably one of the best monographs which has been given to us on the pathology of this very rare condition. If I remember rightly his idea was that the fat was more or less of a metaplasia of connective tissue which might mass itself in a tumor formation or might occur in discrete areas in other uterine tumors, especially fibromyoma. I do not think he was wrong in his interpretation, because those who have had an opportunity of examining many fibromyoma find microscopically some conditions which seem to tend to fat transformation.

## CONCERNING A PHAGE (LYTIC AGENT) ISOLATED FROM TRANSPLANTABLE ANIMAL TUMORS

G. L. ROHDENBURG, M.D.

*(From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director)*

Several years ago d'Hérelle announced that he had been able to isolate from the feces of those recovering from dysentery a substance which had the power of causing lysis of the etiological bacteria. Since that time there have been other publications dealing with various phases of the problem. D'Hérelle applied the term "phage" to the agent capable of causing this lysis.

Phages have been isolated from many sources by at least two technical methods. The phages which have been isolated from bacteria have been more or less specific in their lytic action. The nature of the phage is not yet fully determined. D'Hérelle is of the opinion that it is an ultramicroscopic organism, and the recent work of Salimbeni places the organism as a mycelium; Kabeshima, however, presents evidence which suggests the possibility of its being enzyme in nature. Since d'Hérelle was first able to isolate the lytic substance only from the feces of those recovering from the infection, he suggested that the phage might have something to do with convalescence.

Transplantable malignant tumors in animals are roughly divided into two groups, those which in varying percentage recede spontaneously and those which do not. In spite of many experiments, the cause of this spontaneous recession still remains unexplained. The experiments recorded in this report were undertaken with the idea that spontaneous recession of transplantable malignant tumors might possibly be due to a tissue phage.

The technical steps of the experiments are simple. The tissue to be examined is obtained under sterile conditions and a cube varying from 0.2 to 1 cm. in diameter is placed in broth. The inoculated tube is incubated for a period of forty-eight hours at 37° C. The presence or absence of a phage may be demonstrated by one of two methods. At the end of forty-eight hours' growth, if the broth remains clear, it is plated on nutrient agar, isolated drops of the broth being added to the agar plate just before solidification occurs. In a second method about 0.3 c.c. of the broth is added to a sterile two per cent. suspension of red cells in physiological saline. The agar plate, or the blood tube, are then incubated at 37° C. for twenty-four hours. The presence of a phage is predicated upon either the lysis of the red cells in the saline tube or definite zones of digestion in the agar plate (Fig. 1). If the original broth culture shows bacterial growth after incubation, then it should be filtered through a Berkefeld filter, and the clear filtrate used as previously described.

Following this technic, examinations of all of the twelve

growing tumor strains in the laboratory were made. Each tumor strain was examined twice, and as controls, normal kidney, spleen, and fetal tissue were also examined. A phage was demonstrable in all.

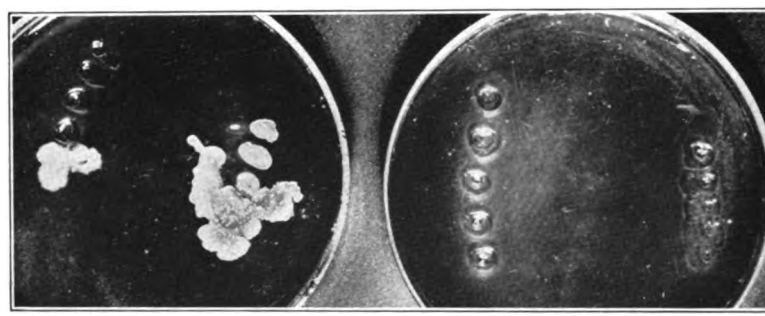


FIG. 1. FIG. 2.

FIG. 1. Pure phage isolated from transplantable animal tumor.
FIG. 2. Phage with intentional bacterial contamination.

The examinations were again undertaken with six receding tumor strains, actively receding tumors being cultured in each instance. A phage was demonstrable in all of twelve attempts. The same technic was then applied to a rapidly growing carcinoma of the breast in the human, and a phage was also isolated.

The following observations have been made on the phage isolated from receding rat and mice carcinomata and sarcomata: Lytic action of the broth culture is demonstrable up to a dilution of 1:1200. The phage can be propagated. The phage passes through a Berkefeld filter, but is not dialyzable through a celluloidin sac. Phage cultures to which red cells have been added show, after seven to fourteen days, a gradual reduction of the hemoglobin to some other pigment derivative. One strain of phage has been propagated for fourteen generations. The addition of alcohol or glacial acetic acid to the broth culture produces a copious flocculent precipitate, which is again partly soluble in physiological saline solution and which still shows phage action after twenty-four hours' contact with the precipitating chemical. The addition of blood to phage cultures has thus far

uniformly resulted in a bacterial growth, the bacterium being a thin bacillus, occasionally occurring in chains, Gram-positive, and showing spores. This organism has not yet been identified; however, when it appears in a phage culture the lytic action of the broth very markedly decreases, or completely disappears. Contamination of phage culture by other bacteria, *i.e.*, staphylococcus, streptococcus, typhoid bacilli, *B. subtilis* and *proteus* does not inhibit or destroy the phage action.

A single injection of nonbacterial contaminated phage broth into animals bearing transplanted tumors which do not spontaneously recede does not cause recession, possibly because the blood present in the body brings about the development of the bacterial growth previously referred to. If any action be demonstrable, it is a stimulation of growth, though this can not be asserted positively. Animals bearing tumors which do not spontaneously recede when injected with the bacterial growth show no decrease in growth energy.

*Discussion:*

DR. NOGUCHI: I would like to ask if you determined the optimum hydrogen ion concentration in which the phage acts.

DR. MACNEAL: I should like to know just what the action is on the agar. I take it these are agar plates to which a drop of this broth has been added. Apparently there is a hollowing out of the agar, and in some instances there seems to be a bubble of air in it. Of course these are formalin preparations, and it is difficult to tell what the original appearance may have been, or what is the interpretation of the change in the agar when it was fresh. Is it liquefaction, digestion of the agar, or what?

DR. WOOD: I would like to ask Dr. Rohdenburg to continue his argument a little further against or for a ferment. As far as my own opinions go, I watched the work with a great deal of interest, and I have not the slightest idea what the explanation is. I think we will have to suspend all judgment until more data have been collected. The phage evidently has nothing to do with the disappearance of tumors, because it is found in progressively growing tumors, and also in human tumors in which there is no possibility of regression.

DR. ROHDENBURG: These experiments are really only at their beginning, and no work has been done on the hydrogen ion concentration. I would add that the phage can be demonstrated by using 200 c.c. of salt solution to which 15 or 20 c.c. of ordinary nutrient broth and a fragment of tumor have been added.

The original appearance of the plates, when fresh, was perfectly smooth, and in those experiments where precipitation was obtained with acetic acid and alcohol, we could see, because of the precipitate, where the drop was placed. After twenty-four hours the surface of the agar was eroded. There was no liquefaction that was demonstrable, though the water of condensation on the plates might be due to the evaporation of the liquefied agar.

DR. MACNEAL: Did you drop the broth on before the agar was solidified?

DR. ROHDENBURG: Just before it was solidified.

---

# THE SIMULTANEOUS OCCURRENCE OF A METASTASIZING HEPATOMA AND AN EPITHELIOMA OF THE ESOPHAGUS

DE WITT STETTEN, M.D.

Since the careful analysis by Harbitz[1] considerable interest has been shown by oncologists in the question of the simultaneous occurrence of multiple tumors—particularly of different neoplasms in diverse organs. It has recently been my fortune to have observed a rather unusual case of this nature, and it was with some trepidation—as I am only a surgeon—that I accepted your secretary's invitation to present this case before your Society.

The patient was a man, fifty-nine years of age. For about a year he had had vague abdominal symptoms, with loss of weight. Shortly before I saw him in October, 1920, he had had several attacks of pain, which resembled biliary colic. On examination, he was decidedly emaciated and a moderately enlarged, slightly nodular liver could be palpated. The gall bladder region was sensitive. There was no jaundice, nor temperature. The blood showed a moderate secondary anemia. The Wassermann test was negative. Radiography showed indirect evidence of gall bladder disease.

The probable diagnosis of carcinoma of the liver was made, but in view of the gall bladder symptoms, and the possibility of an error in diagnosis, an exploratory laparotomy was advised and performed on October 14, 1920. The liver was found diffusely enlarged, the surface was somewhat nodular and irregular in consistency, but it was difficult to find distinct nodes. The liver surface did not suggest a typical carcinoma. One small, definite nodule, lighter in color than the rest of the liver surface, and situated near the liver edge, to the left of the suspensory ligament, was excised for

diagnosis. The gall bladder was found to contain numerous calculi and a cholecystectomy was done. The quadrate lobe felt particularly hard. There was no evidence of a primary growth in the stomach, gall bladder or intestines. There were fine adhesions between the upper surface of the liver and diaphragm.

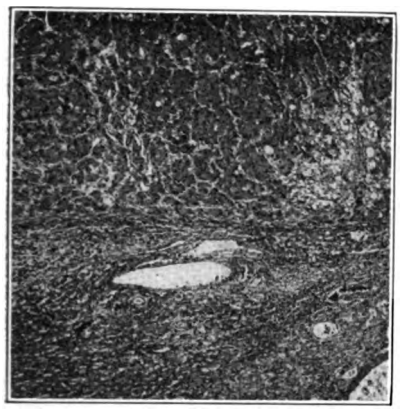


FIG. 1.

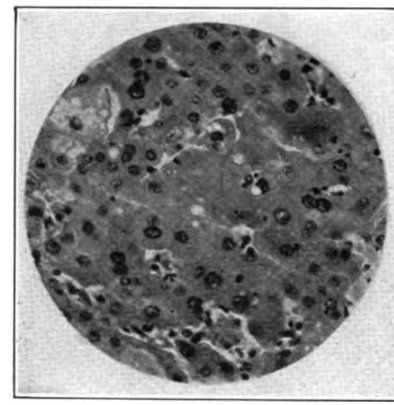


FIG. 2.

FIG. 1. Hepatoma, separated from normal liver by zone of round-cell infiltration. Low power.

FIG. 2. Hepatoma. High power.

Microscopic examination of the excised nodule showed it to be a typical Rokitansky liver-cell adenoma or so-called hepatoma (Figs. 1 and 2). The cells, though they resemble liver cells are much larger, take a deeper stain, and are not arranged in the same orderly fashion. They possess a large amount of granular, acidophilic protoplasm and small vesicular nuclei, which generally show a single nucleolus. There is some variation in the size of the cells and nuclei and large cells with a single, large, or several small nuclei are occasionally observed. Mitosis is not active. In the center of the tumor nodule there is some fatty degeneration of the cells. The tumor is split into larger and smaller, irregular lobules by bands of fibrous tissue, but there is no tendency to form acini, the cords and islands of tumor cells being supported merely by thin-walled capillaries. The growth is partially surrounded by a fibrous capsule, though in one area tumor cells have broken through the capsule and are irregularly distributed among the surrounding atrophic liver cells, and in other places the tumor tissue is separated from the adjacent liver tissue by a zone of round-cell infiltration.

Histologically the tumor seemed to be benign. A Wassermann taken after operation showed 4 plus with natural amboceptor and negative after anti-sheep amboceptor had been added. This suggested the possibility of a syphilitic infection and it was hoped that perhaps the liver condition might be explained on that basis. Sternberg[2] has called attention to the fact that in

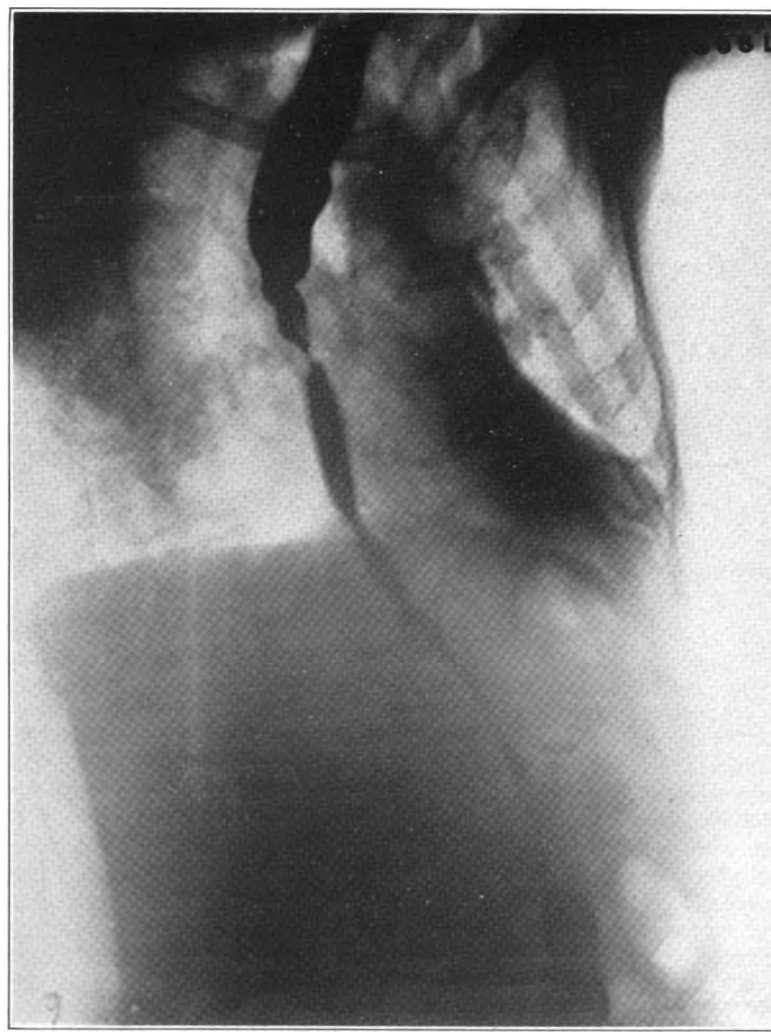


FIG. 3. Radiograph of esophagus, showing obstruction in lower third.

certain forms of nodular adenomatous hyperplasia of the liver, compensatory to various destructive processes, great difficulty occurs in differentiating these lesions from the true adenomata. On this theory and in the hope of arresting further liver destruction, a course of anti-syphilitic treatment was begun, but soon abandoned, as it was not well tolerated and showed no results, and as a subsequent Wassermann was negative.

FIG. 4.

FIG. 5.

FIG. 4. Gross appearance of hepatomata of liver.
FIG. 5. Gross appearance of hepatomata of liver, with large necrotic tumor in center of organ.

About two weeks after operation the patient began to complain of dysphagia. X-ray examination of the esophagus (Fig. 3) and esophagoscopy showed a marked obstruction, undoubtedly organic in character, in the lower third of the esophagus. Whether the lesion was intra- or extra-esophageal could not be positively established, but on November 27, 1920, a gastrostomy was performed. On December 16, 1920, the patient died from asthenia.

Postmortem examination showed the following important changes:

The liver is somewhat enlarged but very much distorted by numerous nodules which project from beneath the capsule (Fig. 4). These nodules are circumscribed, of pinkish-white color, and granular surface. They vary in size from 0.5 to 12 cm. in diameter. About the center of the organ is a large tumor of this type which has undergone complete necrosis, the necrotic material being bile green (Fig. 5). Vascular emboli are demonstrable in the gross, projecting from veins which are visible on the inner wall of the cyst left by the necrosis of the tumor tissue.

Scattered throughout the lungs are pinkish-white, circumscribed nodules ranging in size from a pin-head to 2 cm. in diameter.

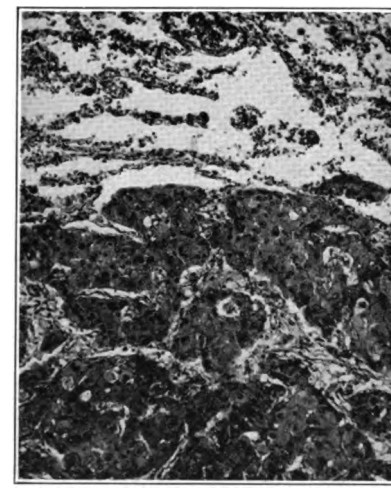
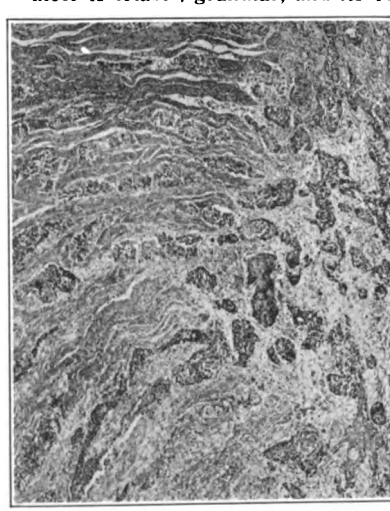


FIG. 6. FIG. 7.

FIG. 6. Gross appearance of squamous-cell epithelioma of esophagus.
FIG. 7. Metastases in lung from hepatoma.

The esophagus shows, approximately 16 cm. from the cardia, a stenosing ulcer, involving over three-quarters of the circumference of the tube and measuring 3 x 2.5 cm. in its greatest diameters (Fig. 6). The base of this ulcer is friable, granular, and its edges are not indurated.



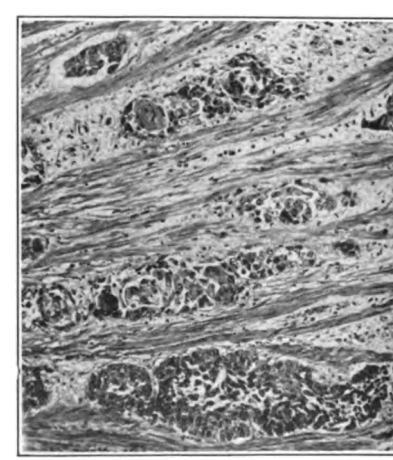


FIG. 8. FIG. 9.

FIG. 8. Squamous-cell epithelioma of esophagus. Low power.
FIG. 9. Squamous-cell epithelioma of esophagus, showing pearl formation. High power.

The microscopic examination of the tumors of the liver (Figs. 1 and 2) and of the nodules in the lung (Fig. 7) shows them to be of the same character as the nodule originally excised for diagnosis at the first operation—namely, liver-cell adenoma or hepatoma, primary in the liver and metastatic in the lung. In the liver tumors blood vessel emboli are demonstrable and there is extensive degeneration and necrosis in many of the neoplastic areas. Elsewhere the liver shows a mild degree of cirrhosis of the intralobular type.

The ulceration in the esophagus shows a necrotic surface beneath which are islands and columns of epithelial cells of the stratified, squamous variety in which intercellular bridges and occasional pearl formation are demonstrable (Figs. 8 and 9). These neoplastic cells have invaded the muscle to a considerable depth. The lesion has all the characteristics of a typical squamous-cell epithelioma of the esophagus.

In conclusion, I wish to acknowledge my indebtedness to Drs. G. L. Rohdenburg and F. D. Bullock for their help in the pathological study.

*References*

1. HARBITZ: Ueber das gleichzeitige Auftreten mehrerer selbständig wachsender ("multipler") Geschwülste, *Beitr. z. path. Anat. u. z. allg. Path.*, 1916, lxii, 503.

2. STERNBERG: Aschoff's Pathologische Anatomie, 1913, Ed. 3, II, 894 and 901.

*Discussion:*

DR. ROHDENBURG: A number of years ago I presented a series of tumors primary in the liver, some of the gall bladder, and others of the liver cell type, and I was particularly anxious to have Dr. Stetten present this case here to-night, because at that time Dr. Ewing said one of my cases was unique in that there were metastases in the lymph nodes, and that he had never seen metastasis in a carcinoma of the liver of the hepatoma type. This particular case emphasizes that metastases do occur much more beautifully than the cases I showed.

DR. SYMMERS: Was there evidence of bile staining?

DR. STETTEN: The necrotic central tumor was bile stained.

DR. WOOD: This is an extraordinarily interesting case because it illustrates very well the question of malignancy of tumors of this type. The primary growth in the liver does not differ from the adenomata seen in cases of cirrhosis, and the carcinoma in the lung is also very close to the type we find similarly associated. The tumor shows how little morphology has to do in the determination of the malignancy of some of these adenomatous neoplasms. This is well known in connection with the thyroid tumors which may metastasize and form nodules of tissue very closely resembling normal thyroid. It is impossible to believe that without metastases such tumors are malignant. There was a little bile in some of the metastases in the lung. This is very interesting more from the general point of view of

the nature and the biological qualities of the cells. Here is a liver tumor which is malignant because it has metastasized, but the cells of which are so slightly altered from the normal liver cells that they are still able to perform a considerable function, and it is difficult to consider that their chemistry and their general biological nature are very different from the normal liver cell. I think we are all coming to the realization that the cells of a carcinoma and the cells of the original tissue from which the tumor is derived are only slightly different. At the Crocker Laboratory we are doing experiments all the time to attempt to find out some differential point between the carcinoma cell and its homologous tissue, and the more we work the less difference we find. A long series of experiments have been carried out on the question of the hydrogen ion reaction of tumor cells and the homologous tissues, and we do not find any differences. It is well known that there are no general serum reactions following the growth of a tumor. The old belief of the production of cachexia by a tumor toxin is now practically abandoned. We see animals carrying tumors corresponding to one or two feet in diameter in the human being. Such animals are not in the slightest degree cachectic, and show no evidence of ill health except that they have a large lump. Pathologists are being forced gradually to the conclusion that the difference between the carcinoma cells and the homologous normal cell of the same growth rate is most minute and escapes all analysis.

DR. LARKIN: I think the simultaneous occurrence of different types of tumor in the same individual is not at all uncommon. The occurrence of simultaneous tumors of different types was pointed out by Virchow, and it has been my privilege to study a number of such tumors. From the description which Dr. Stetten gives, especially as regards the liver tumor, it would seem to me that that tumor is unusual, and is really a hepatoma.

The simultaneous occurrence of the epithelioma of the esophagus is rather unusual, and it is worthy of great attention. It may be interesting to know that only this afternoon we had an individual brought to the hospital with a very large tumor and there was a section made from the liver on which a diagnosis of primary carcinoma of the liver was made, probably an adenocarcinoma of the gall bladder ducts. There was nothing found in the abdominal cavity except this very large tumor. The stomach seemed to be normal.

DR. STETTEN: I want to say a word about the question of cirrhosis. I was much more interested in this case from the surgical and therapeutic standpoint than from the pathological, and when we first excised the nodule and the report was received, I tried to persuade Dr. Rohdenburg that maybe we were dealing with one of those adenomatous nodules found in the hyperplasias, compensatory to destruction of the liver, and I even gave him some references to an article by Sternberg in Aschoff's Pathology, in which he distinctly says it is often impossible to differentiate these lesions from true adenomata. Dr. Rohdenburg was willing to admit that perhaps this was so. When we obtained the 4 plus Wassermann with the natural amboceptor we gladly accepted syphilis as the cause of the trouble, and hoped that we

were going to cure the man by giving him anti-specific treatment. After the first operation he actually improved somewhat and appeared to be getting better. I was interested in presenting the case, not so much on account of the nature of the liver tumor, but because of the simultaneous occurrence of the two different types of malignant tumor, suggesting that the patient exhibited a distinct tumor diathesis, upon which Virchow laid so much stress years ago.

---

## DEMONSTRATION OF LEPTOSPIRA ICTEROIDES, WITH NOTES ON THE RESULTS OF PROPHYLAXIS AND SERUM TREATMENT OF YELLOW FEVER

HIDEYO NOGUCHI, M.D.

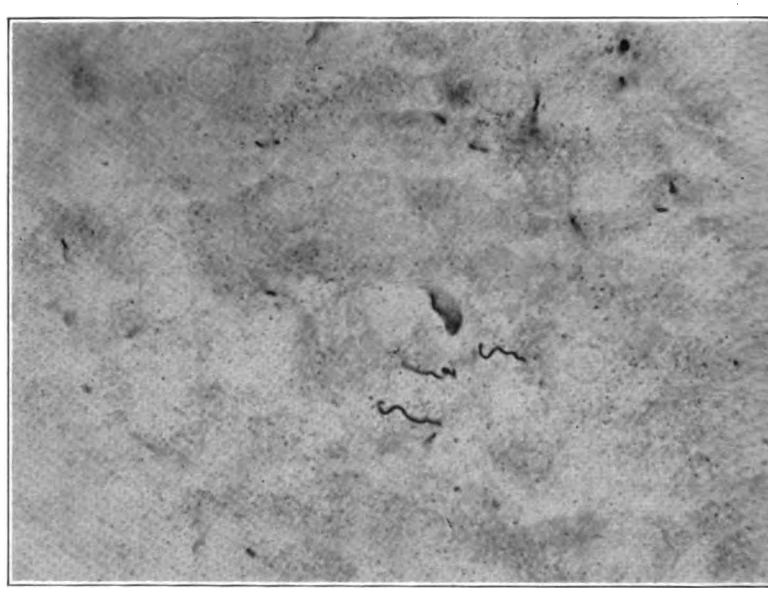
*(From the Laboratories of the Rockefeller Institute for Medical Research)*

*Leptospira icteroides* was first isolated in 1918 from cases of yellow fever in Guayaquil by the speaker; later the organism was obtained from yellow-fever cases in Mérida, Yucatan (Noguchi and Kligler, 1919) and in northern Peru (Noguchi and Kligler, 1920). The finding was also confirmed in Mexico by Dr. Perez Grovas, in Vera Cruz in 1920, and by Le Blanc of the Rockefeller Institute in the same city in 1921. Gastiaburú, of the Instituto de Higiene of Lima, transmitted yellow fever to guinea pigs from cases occurring during an epidemic in Piura, Peru, in 1919.

The killed cultures of *Leptospira icteroides* were first used for protective inoculation against yellow fever in Guayaquil in 1918, where 427 vaccinations were carried out. The results were so encouraging (the morbidity rate among vaccinated and unvaccinated during the same period being 11 and 110 per thousand respectively) that a vaccine several hundred times stronger has been made in large quantities and employed in Mexico and various Central and South American countries, the total number of non-immune persons reported vaccinated being about eight thousand. The development of protection, as in the case of all vaccines of this kind, requires about ten days for completion, and persons exposed to yellow fever just before vaccination or immediately afterwards are not protected by vaccination. Exclud-

ing such instances; however, there has been no case of yellow fever among the eight thousand vaccinated in the various localities, while among unvaccinated persons during the same period and in the same areas there have been about seven hundred cases of the disease.

The use of vaccine furnishes a rapid method of elimination of non-immune persons from areas where yellow fever is epidemic. By the application of sanitary measures to eliminate the mosquito carrier and vaccination in the meantime to cut off the supply of non-immune material from the infected mosquitos, a threatening epidemic of yellow fever in Guatemala and Salvador in 1920 is reported to have been checked within one month from the appearance of the first cases, that is, before a second set of



*Leptospira icteroides* in the liver of the guinea pig. Guayaquil strain. × 1,000.

cases had developed. The value of vaccination as an emergency measure does not, however, minimize the importance of the anti-mosquito operations, since both factors—the non-immune human being and the infected mosquito—must be eliminated in order to eradicate yellow fever.

A therapeutic serum is also available for treatment of yellow fever. It has already been employed in 170 cases, and persons treated before the third day of illness have almost invariably recovered, the exceptions being those cases in which the quantity of serum used was too small to have any effect. By the fourth day of illness the injuries to organs are so great as to be irreparable in severe cases of yellow fever. The usual mortality in yellow fever, fifty to sixty per cent., has been reduced to 13.6 per cent. by the use of the serum.

The records of vaccination and serum treatment presented here comprise the work of a number of observers. The initial vaccination experiments in Ecuador were carried out with the cooperation of Dr. Pareja and the Direccion de Sanidad of Guayaquil; the statistics from Central America cover the work of Drs. Lyster, Bailey, and Vaughn; for the records of Mexican cases I am indebted to the Consejo Superior de Salubridad (Drs. Vasconcelos and Casasús), to the Junta de la Sanidad de Yucatan (Dr. Hernandez), and to Dr. Le Blanc; the Tuxpan statistics were furnished by Drs. Lynn and Guadarrama; the work in Peru was done with the cooperation and assistance of Dr. Kligler and Peruvian health authorities.

---

## A COMPLEMENT FIXATION TEST OF VALUE IN THE CLINICAL DIAGNOSIS OF TOXIC THYROID STATES

WILLIAM N. BERKELEY, M.D.

A scientifically exact method for the clinical diagnosis of plus, minus, and toxic thyroid states would be a great boon to clinical medicine; and the problem is not insoluble, but the solutions heretofore suggested are not entirely satisfactory.

E. C. Kendall,[1] among others, has proposed the basal metabolism as a guide to the existence of hypo- and hyper-thyroid conditions. But apart from the expense and complicated pro-

cedure of this method is the objection that no one yet knows how many other clinical conditions may temporarily influence the basal metabolism in both plus and minus directions. The advocates of this method, as it makes no provision for thyroid toxins, dispose of the matter by denying the existence of such bodies.

E. Goetsch[2] has suggested the severity of the patient's reaction to a measured hypodermic dose of adrenalin as a measure of his thyroid activity. I can not learn that this test has proved generally confirmatory of evident clinical signs. One medical friend of mine with large clinical experience thinks it a dangerous method, causing sometimes a violent and alarming reaction. M. S. Woodbury,[3] in a study of some fifty recent cases of thyroid disease at Clifton Springs, N. Y., concludes that the adrenalin test is an indicator of "general sympathetic hypersensitiveness" which may or may not be of thyroid origin. Further reports[5], [6], [7], from other observers are unfavorable.

It was my idea at one time that if the thyroid secretion appears in the blood in a protein form (it seems generally agreed that it is in protein form in the thyroid gland), it might be picked up by a complement fixation test and titrated. In order to try out this supposition the following experiment was repeated a number of times: A healthy young sheep was immunized by successive injections of a saline suspension of thyroids from freshly killed dogs. Using the injection as antigen, a pronounced and abundant antibody could be demonstrated in the sheep serum in the course of a few injections. But not the slightest binding could ever be observed with normal dog serum as antigen. This seems to prove either that the thyroid secretion is not present in the serum at all in protein form, or that, if so, it is in too minute amount to be available for a fixation test. As I have not found any mention in the literature of such an experiment as this, it seems worth while to record it even in its present fragmentary form.

Failing in this attempt, my attention was turned to the possibility that when the chemistry of the thyroid gland is materially disturbed, as in exophthalmic goiter, the thyroid toxins (assum-

ing for the time that such bodies exist) might be accessible to study by the same (complement fixation) method.

There is almost no literature on this subject that I have been able to find, except some pioneer work done almost ten years ago by Prof. Marinesco, and his associate, A. Papazolu.[4] The latter of these observers claims to have found antibodies a number of times in the serum of patients suffering from Basedow's disease. He used as antigen aqueous, alcoholic, and ethereal extracts of Basedow goiters, parenchymatous goiters, and normal thyroids. Of his 38 tests 14 showed complete fixation, 12 almost complete fixation, and 12 were negative.

This work, while interesting and suggestive, dates back to the very early days of scientific serology, and seems not to have been very carefully controlled. Moreover, Papazolu used alcoholic and ethereal as well as aqueous extracts of his thyroid antigens, thereby, of course, getting fixation with many luetic subjects.

Using non-lipoidal antigens (for method of preparation and serological technique, see Mr. Koopman's note) derived from various thyroid tumors (about ten in all), it has been impossible to get fixation with the serum of Graves' disease except in the case of a single goiter kindly given us by Dr. John Rogers. This growth Dr. Rogers thought to be a true Graves' tumor. Unfortunately it was all extracted, nothing being left for microscopic examination. Antigens from four normal human thyroids gotten at autopsy under favorable conditions entirely failed to bind.

About this time, through a fortunate combination of circumstances, Mr. Koopman observed that with *normal dog thyroid* random samples of Basedow serum would bind powerfully, and that they would not bind with any other dog organ.

Starting out with this test as a guide—*i.e.*, using dog thyroid as antigen—fixation experiments have been done on more than 195 human serums, of which 44 were under suspicion of positive thyroid dyscrasia.

Of the 44, 18 were clinically undoubted Graves' disease, 2 were probably so, 14 were doubtful, and 10 were probably *not*

Graves'. I have full notes of most of these cases; in all the instances where the blood only was sent (through the courtesy of medical friends kindly interested in the research) the diagnosis was made by a colleague in whom I had unusual confidence. I believe the chances of error in this regard are reasonably remote.

The 18 Graves' cases were all one plus to four plus. The probable cases were positive; 10 of the 14 doubtful cases were positive; the ten "probably not" were all negative.

As to the controls, numbering over 140 patients, all were negative except one. This exception was a young married woman of about thirty years, with a tertiary specific skin lesion on one knee. She was not particularly nervous; her pulse was 96; her eyes and thyroid did not strike one as pathologically prominent. She had a positive Wassermann and a positive thyroid fixation. She was lost before it was possible to make any further investigation of her history and condition. All the other controls—representing nearly all the chronic and many of the common acute diseases (non-infectious)—were, as already noted, negative. About 20 were old fibrocystic goiters. About 20 more were puberty enlargements. Serum kindly sent us by Dr. George Draper from a borderland case was, he reported, negative to the Goetsch test; we found it two plus positive to the dog thyroid test. Another serum (Dr. Jos. H. Fobes) was positive to the Goetsch test, and also two plus with dog thyroid.

The new test has been repeated hundreds of times and has been checked up with all needful controls. If anyone alleges that the binding is due merely to the chance appearance in human serum now and then of a native amboceptor, then he must also explain why in more than ninety-five per cent. of the cases the native amboceptor appeared in patients with a positive thyroid dyscrasia.

Speaking further for the value of the test is the fact that in several of the positive cases which have improved very much or apparently gotten well in the last eighteen months, the test has varied concomitantly with the clinical improvement, falling from four plus to two plus, and later disappearing entirely. Dr. H. H.

Janeway, of the N. Y. Memorial Hospital, who has recently experimented extensively with radium in these cases, tells me that he considers the test of distinct value in the quantitative adjustment of such treatment to the clinical condition of the patient.

The number of cases so far observed is too small to make the suggestion more than tentative, but with this reservation I venture to hope that the new test may be found of value in several directions:

1. In the clinical diagnosis of a great many cases which are now very perplexing—early cases, late cases, borderland cases, anomalous cardiac neuroses, and thyroid tumors without definite signs of thyroid poisoning, such as unusual menstrual swellings, post-puberty enlargements, and fibrocystic goiters in the early stages. Such a test would help to differentiate exophthalmos due to other causes than Graves' disease, and would eliminate many cases of severe tobacco poisoning due to cigarettes, where the symptoms and signs (as recently noted in army soldiers and recruits) have been such as to deceive the very elect.

2. The test would aid in the adjustment of therapeutic measures to the immediate condition of the patient.

3. The test is simple, inexpensive, and absolutely harmless.

4. And finally it might throw considerable light upon the etiology of cellular tumors in general.

Subject to later modification the view may be suggested that spontaneous recovery in exophthalmic goiter is due directly to the formation of these corrective antibodies in the patient's own system; and that rest, careful feeding, and relief from anxiety contribute to the cure merely by aiding the patient's normal immunity-mechanism.

*Bibliography*

1. KENDALL, E. C.: *Journal A. M. A.*, 1918, lxxi, p. 871, and *passim* in recent medical literature.
2. GOETSCH, E.: *N. Y. State Journal of Medicine*, 1918, xviii, p. 259.
3. WOODBURY, M. S.: *Journal A. M. A.*, 1920, lxxiv, 997.
4. PAPAZOLU, A.: *Séances et Mémoires de la Soc. de Biol.*, 1911, lxxi, 671.
5. SANDIFORD, IRENE: *Am. Jour. Physiol.*, 1920, li, 407.
6. MARINE, D., AND LENHART, C. H.: *Am. Jour. Physiol.*, 1920, liv, 248.
7. MAYO, C. H.: *Journal A. M. A.*, 1921, lxxvii, 353.

# TECHNIQUE OF COMPLEMENT FIXATION REACTION IN BASEDOW'S DISEASE

JOHN KOOPMAN

The blood of some patients who show symptoms of Basedow's disease binds complement in the presence of an antigen made from normal thyroid glands.

The reaction may be due to a specific thyroid substance which combines with an antibody in the blood of the patient.

The best method of preparing the antigen which we have been able to find is as follows: The glands are obtained under aseptic precautions as soon as possible after the dogs have been killed. Each gland is trimmed carefully and minced finely with sterile scissors. The whole mass is then ground in a mortar with a measured quantity of washed and sterilized sand and of dry sodium chloride. The amount of sand is of no importance, but the salt should be added in the proportion of 1/10 gram to each gram of gland used; a few drops of 2 per cent. aqueous solution of tricresol are added for each ten grams of thyroid. This mixture is bottled and laid away in the ice-box. For use it is made up with distilled water, using 10 c.c. of water to one gram of the original amount of gland. The sand and solid matter are removed with the aid of a centrifuge.

It is best to use the mixed glands of five or six dogs. As at present prepared, the extract contains much extraneous matter which takes no part in the reaction; if some method of securing the antigenic substance free from all foreign matter could be devised, the specificity would be enhanced. As far as we have gone, we know that the antigen slowly deteriorates even when kept under the best conditions, and after about three weeks it is necessary to obtain a new supply. Drying instantly spoils its antigenic properties and it does not withstand heating to 50° C. for fifteen minutes.

The test is set up in the form of a titration, using a constant

amount of serum which is not more than one quarter of the least amount which is anticomplementary. The antigen is used in varied amounts, beginning with an excess and ending with the least amount which can be expected to give fixation. The exact amounts used will depend upon the total volume of the test the worker is accustomed to using. At the same time an antigen control is made with the same quantities of antigen as are put in the test. This procedure will obviate the necessity of putting in a separate titration of the antigen before the test itself is made. The result is indicated by the difference between the quantity of antigen which is anticomplementary of itself and the quantity which binds complement in the presence of serum. A negative serum with the antigen will often bind less complement than the antigen alone.

A serum is considered positive when it binds complement in the presence of one half or less than one half of the anticomplementary dose of antigen, and the smaller the amount of antigen necessary for complete fixation the stronger is the reaction. Fixation is carried out for from four to six hours in the ice-box. At the present time the range is short, but with improved methods of preparing the antigen it is hoped the range will become greater.

Besides the tests on human glands and human tumors (*i.e.*, thyroid tumors), as above mentioned, we have tried the glands of some other animals, namely, guinea pig, bullock and pig, and we find that guinea-pig glands give results comparable with the dog antigen.

Much more work also remains to be done on fixation results with extracts of true exophthalmic goiters. These are now very hard to get in New York operating rooms, as surgical removal of them has gone out of fashion; and we have not been able to devise any way of keeping them in fit condition for antigen formation for more than two or three weeks.

*Discussion:*

DR. NOGUCHI: Was the fixation complete?
MR. KOOPMAN: Yes.
DR. NOGUCHI: How much serum was used?

MR. KOOPMAN: Not more than about one-fifth or one-sixth of the anti-complementary amount.

DR. NOGUCHI: In absolute quantities, what would that be?

MR. KOOPMAN: Using 0.10 c.c. of 10 per cent. complement that would be about 5/1000 c.c.

DR. NOGUCHI: Do you find many human serums anticomplementary?

MR. KOOPMAN: With ordinary cases perhaps one or two per cent. of the sera will be anticomplementary; and of fresh sera not more than one-tenth of one per cent.

---

# PROBABLE SYPHILITIC INTERSTITIAL PNEUMONIA IN AN ADULT

ROLFE FLOYD, M.D.

Syphilis of the lung took a definite place in medical literature about one hundred years ago, and from that day to this it has always been a difficult and often an uncertain diagnosis for the pathologist. Clinicians, on the other hand, have not hesitated from time to time to make the diagnosis easily and often, especially about 1880, when syphilitic phthisis was a frequent complaint, curable at certain European Spas, and again very recently, when X-ray lung shadows which diminish after antisyphilitic treatment, particularly if associated with a positive Wassermann, are considered, with altogether unwarranted assurance, to be a sufficient basis for the diagnosis. Rössle, a present German writer, considers syphilis of the lung as frequent as syphilis of the liver, and Carrera,[1] working in Warthin's laboratory, considers its incidence similar to that of syphilis in the other internal organs. The average incidence, however, reported by competent pathologists of wide experience is about one or two cases per thousand autopsies.

The discovery of the *spirochæta pallida* has failed to throw the expected light on pulmonary syphilis, because it has proved practically impossible to demonstrate this organism in the lungs of adults; Koch and Schmorl[2] and Warthin being the only ones to find it so far.

It is thus a peculiar fact that a generation after the discovery

of the tubercle bacillus, and half a generation since the discovery of the causative agent of syphilis, the diagnosis of syphilis of the lung still rests primarily on pathological anatomy.

Gummata of the lung, both in infants and adults, are accepted as definitely luetic, though sometimes difficult to distinguish from tubercular lesions. Again the so-called white pneumonia of infants is considered syphilitic by practically all observers.

It is concerning interstitial pneumonias of adults that it is the hardest to say whether they are syphilitic or not, for this condition results from many causes besides lues; thus persistent broncho-pneumonia, lobar pneumonia followed by fibrous organization, certain forms of pulmonary tuberculosis, invasion of the lung by inflammatory connective tissue from the pleura, the peribronchitic indurations that occur with prolonged irritation by dust, some extreme types of chronic congestion and unusual changes produced by foreign substances, as in broncho-esophageal fistula, may all result in extensive interstitial changes in the lung parenchyma.

Accumulating experience, however, has gradually established the following as the characters on which an adult interstitial pneumonia is to be judged syphilitic:

1. The presence of tertiary syphilitic lesions in other organs. This is a most important criterion, as well as one of the first to be recognized. In the absence of such a lesion extreme conservatism must be exercised in considering an adult interstitial pneumonia syphilitic.

2. Gross characters of syphilitic interstitial pneumonia, which are: (*a*) location in the lower lobes; (*b*) white fibrous foci, often multiple and more or less confluent with large and small radiating fibrous bands which may reach the pleura and cause a coarse puckering of it through contraction; or similar bands arising as direct extensions of the inflammatory connective tissue wall of ulcerated and stenosed stem bronchi; (*c*) the absence of necrosis and of calcification.

3. Microscopic characters, which are more diagnostic than the gross and consist of: (*a*) an extensive inflammatory over-

growth of the pulmonary connective tissue framework, the new tissue at first full of fibroblasts and thin-walled blood vessels, later becoming more densely fibrous; (*b*) round cells scattered through this tissue especially in foci and most typical when in perivascular concentrations. The alveoli, as in interstitial pneumonia of other types, are often reduced to small spaces lined by cuboidal epithelium. Sclerosis of the arteries is frequent. Giant cells are much less frequent than in tuberculosis, while miliary gummata and necrosis are not described in this form. Masses of smooth muscle mixed in with the new areolar connective tissue have been noted by Tanaka.[3] The amount of anthracosis and of elastic fiber destruction are still matters of dispute.

A complete bibliography and an extensive review of the literature is given by Carrera,[1] to whose paper the reader wishing such information is referred.

It is evident that no diagnosis can be considered beyond question on such relative grounds, and that its probability will depend on the number and importance of these features present in each particular case. It is with full realization of this uncertainty that the following case is submitted for consideration.

A woman thirty-four years old was brought into Bellevue Hospital with a general septic peritonitis of which she died three days later. Signs of consolidation and pleurisy were found over the right lower lobe, and it was supposed she had a lobar pneumonia (especially as an exploratory puncture yielded no fluid). There was an artificial anus in the left iliac fossa which she said had been made at the New York Hospital three years previously to relieve an acute obstruction. She had been told at that time that she had a tumor of the rectum, and examination at Bellevue revealed a tight stenosis.

A hæmolyzing streptococcus was found in the blood during life and also cultivated from the spleen after death.

There is no mention of a Wassermann reaction.

The autopsy, done seven hours after death, showed principally: general septic peritonitis and septicæmia; interstitial pneumonia of the right lower lobe with acute fibrinous pleurisy over it; syphilitic stenosis of the rectum, and a large fatty liver.

The right lower lobe contained but little air; it was congested and contained numerous white fibrous foci, more or less confluent in places, from 0.5 to 1 cm. in diameter, from which white strands radiated, some of them reaching the pleural surface. These zones were most numerous below and behind (Fig. 1). There was no fibrosis near the root nor any

lesion of the trachea and large bronchi except recent congestion. The overlying pleura showed an exudate of recent fibrin but was not puckered, or thickened or adherent.

FIG. 1. A small piece of the right lower lobe showing the white, fibrous zones. Natural size.

There was an annular ulcer of the rectum, starting at the anus, extending three inches upwards, and limited by a worm-eaten edge above. Massive thickening of the rectal wall beneath the ulcer caused stenosis almost to the point of occlusion.

Under the microscope the white zones in the lung consist of fibrillated and areolar connective tissue with many elongated nuclei and also many of dumb-bell and other irregular forms. The tissue is well supplied with thin-walled blood vessels (Fig. 2).

Round cells occur all through it, often in distinct foci which frequently show the remnants of a compressed bronchiole or alveolus in the center (Fig. 3). Perivascular round-cell concentrations also occur, but they are not as large or distinct as those found independent of vessels.

Pus cells lie scattered through the connective tissue, probably incidental to the general sepsis.

Compressed alveoli, oval or slit-shaped and lined by cuboidal epithelium, are fairly numerous; if a lumen persists it often contains pus cells (Fig. 3).

Bronchial remnants with higher epithelium huddled together so as to obliterate the lumen also occur; remnants of smooth muscle may be seen about them.

Arteries do not penetrate far into the new tissue. Those on the periphery often are surrounded by round cells, as already described. They show little or no sclerosis.

The lung tissue between the new connective tissue zones is airless, collapsed and congested, the collapse due either to pressure by the expanding connective tissue or to atelectasis resulting from occlusion of bronchioles.

Van Gieson's stain brings out the interstitial connective tissue zones clearly and their rather abrupt transition to areas of collapsed lung.

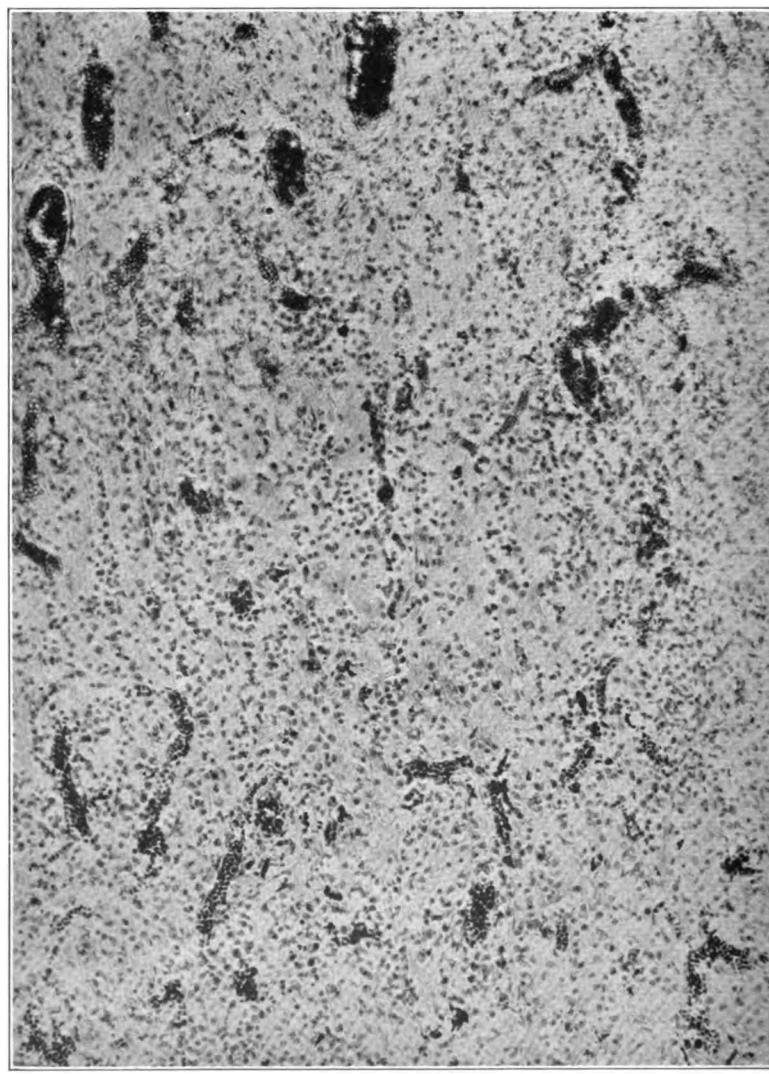


FIG. 2. Fibrillated vascular connective tissue from one of the fibrous zones.

Sections stained by Warthin and Starry's recent improved method showed no spirochætes.

The rectal wall shows, in its deeper layers, sclerosis of the larger vessels and an infiltration of round cells in the perivascular spaces of both large and small vessels. The muscle bundles are separated by fibrous

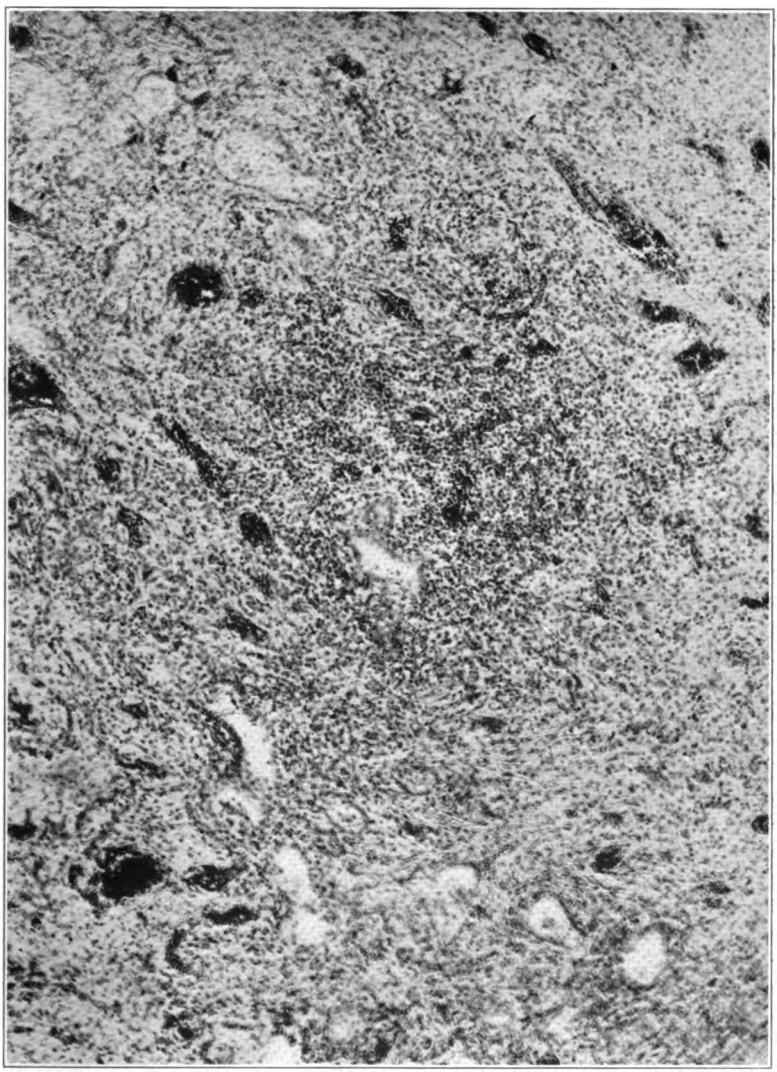


FIG. 3. A round-cell focus in the new fibrous tissue, centering about a compressed alveolus lined with low cuboidal epithelium. Other similar alveoli may be seen beyond the margins of the round-cell focus.

strands which are also densely infiltrated with round cells. The more superficial layers are enormously thickened and changed into firm fibrillated tissue, very densely infiltrated with round cells, continuous with a surface layer of granulation tissue, entirely devoid of all traces of mucosa.

The liver shows a decided amount of fat in the hepatic cells and a distinct infiltration of round cells along the portal canals with a tendency to form foci. There are also pus cells along the portal canals and through the sinusoids.

The reasons for thinking this interstitial pneumonia syphilitic are: (1) the presence of typical syphilitic stenosis of the rectum and probable syphilis of the liver in the same body; (2) the situation of the interstitial pneumonia in the lower lobe, the presence of multiple white foci with radiating bands, without necrosis or calcification; (3) the enormous growth of vascular interstitial connective tissue containing many round cells in foci and perivascular concentrations.

*References*

1. CARRERA: *Am. Jour. Syphilis*, 1920, iv, 1.
2. KOCH AND SCHMORL: *Verhandl. d. deutsch. path. Gesellsch.*, 1907, 2 Tag.
3. TANAKA: *Virchow's Arch. f. path. Anat.*, 1912, ccviii, 429.

*Discussion:*

DR. MOSCHCOWITZ: Dr. Floyd's remarks have offered me considerable consolation. I have a specimen in my possession which I believe is syphilis of the lung, but I hesitated to present it here because I never could demonstrate the spirochete. This lung was found in a patient in whom syphilitic lesions were found elsewhere in the body. She had a syphilitic pancreatitis and a syphilitic perihepatitis. The lower lobe of the lung was completely solid with interstitial pneumonia. I am also fully in accord with what Dr. Floyd said about the clinical diagnosis of syphilis of the lung. That diagnosis is very frequently made. If a patient has clinical symptoms of a pulmonary lesion, and a positive Wassermann is found and an X-ray shadow is present which disappears after salvarsan treatment, the diagnosis is put down as "syphilis of the lung." A close analogy is that of syphilis of the stomach, which is also a frequently made diagnosis. Cases are reported with gastric symptoms and a positive Wassermann reaction, and if under anti-syphilitic treatment the patient gets well, the diagnosis is made of syphilis of the stomach. I think the majority of us would say that syphilis of the stomach is probably one of the rarest lesions found on autopsy.

# MALIGNANT TUMORS OF THE LUNG

A. V. ST. GEORGE, M.D.

(*From the Pathological Laboratories, Bellevue Hospital, New York*)

Primary neoplasms of the lung and associated structures have always been considered a great rarity. Isaac Adler, in 1912, called attention to an apparent increase in primary lung tumors and in the past year or two case reports have been noted more often in medical literature. The increase in the number of cases at Bellevue Hospital seems to bear out Adler's observation.

In Bellevue Hospital, during a period of ten years ending July, 1917, there were three primary lung neoplasms autopsied; from July, 1917, to July, 1919, there were two patients with new growths of the lung coming to autopsy. On the other hand, during a period of twenty months from July, 1919, there were autopsied one case of primary sarcoma of the lung, four cases of primary bronchial growths, one adenocarcinoma of the lung, and one adenocarcinoma of the lung arising from the smaller bronchioles. These seven cases have been made the subject of a paper to be published and are, therefore, merely abstracted here.

*Case 1.* A case of primary lung sarcoma, presented before this society in March, 1920 (published in the *Proceedings of the New York Pathological Society*, N. S., vol. 20, Nos. 1–5, January–May, 1920), and recorded as an alveolar lung sarcoma.

*Case 2.* The patient was a man forty-nine years of age, married, colored, a janitor by occupation, who was admitted to Bellevue Hospital on January 30, 1920, and died February 11, 1920. The onset of his illness occurred four weeks previous to admission, characterized by severe pain in the upper right part of the chest, in the infraclavicular region, of short duration but recurring at frequent intervals; the patient also suffered from severe dyspnœa for three weeks. The family history was irrelevant.

*Physical Examination:* The right eye was absent (removed seven years ago because of trauma); the left eye showed arcus senilis and the pupils reacted sluggishly to light. There was no marked asymmetry of the chest and no expansion on the right side. Dullness was present over the entire right lobe; there were no breath sounds and vocal fremitus was diminished. The left lung was resonant, the breath sounds normal, and there were a few sibilant râles at the base posteriorly. The apex of the heart was palpable in the fifth

space, 17 cm. to the left; there was no enlargement at the base. A long, soft systolic murmur was heard at the apex; the pulse was of poor quality. There were a few old scars present over the tibiæ; knee jerks were not obtained. Thoracentesis showed bloody pleural fluid (not examined microscopically); the urine was normal and the sputum negative for tubercle bacilli; Wassermann reaction was negative. X-ray showed an effusion into the right pleural cavity. The temperature varied between 98.8° and 100° F.; respirations 24 to 32; pulse 80 to 120.

*Diagnosis:* Chronic endocarditis; myocardial insufficiency with decompensation.

*Autopsy* (abstract of protocol): The left lung was easily removed and was voluminous. The pleura was glistening and free from adhesions and exudate. The lung pitted on pressure and was cottony to the touch. It cut with difficulty and the cut surface was dry. The right lung was removed with difficulty due to fibrous adhesions which were especially firm posteriorly. Between the visceral and parietal layers there were about 200 c.c. of bloody fluid and partly clotted exudate, which showed a network of fine fibrin. The pleura was enormously thickened, dense and white. The lung was large, greatly increased in weight, solid and non-crepitant throughout. On section, the upper lobe contained a large, irregularly shaped tumor, which presented a variegated appearance, and was yellow, reddish-yellow and gray in color, extremely soft and friable. It bulged from the cut surface. The tumor occupied almost the entire upper lobe, there being only an area of about 1 to 2 cm. of lung tissue surrounding the tumor. This tissue was solid, non-crepitant and, on section, gray and rough, as was also that of the lower lobe. The alveoli on pressure exuded quantities of thick, cream-colored fluid. The bronchi were congested, but showed no other naked eye changes. The peribronchial lymph nodes were enlarged and, on section, showed a white friable tissue, probably metastatic tumor tissue.

*Anatomical Diagnosis:* Right lung—hemothorax; thickened pleura; fibrinous pleuritis; primary carcinoma of upper lobe; lobular pneumonia of lower lobe. Left lung—emphysema.

*Microscopic Examination:* Microscopically, the tumor in the lung showed small epithelial cells, fairly uniform in size, with many mitotic figures, solidly filling most of the lung alveoli; only here and there were there remains of unoccupied lung alveoli. Microscopic diagnosis: Carcinoma, arising from the alveolar epithelium of the lung.

*Case 3.* The patient was a man sixty-one years of age, Scotch, married, a carpenter by occupation, who was admitted to Bellevue Hospital on April 24, 1920, and died June 27, 1920. He stated that he had had a chronic winter cough for years; malaria twenty years ago; five years ago complete blindness, diplopia; influenza one year ago with sudden onset, pain in chest, fever, and cough for seven weeks. Marital history: wife and five children living, one child died in infancy, cause unknown. Habits: bowels regular, occasionally nocturnal urination is excessive; coffee taken, occasionally alcohol; tobacco; one pound per month. Family history: mother

and father dead, latter at ninety years of age; two brothers and one sister alive and well.

In the middle of December the patient began to cough and expectorate and feel tired. This progressed gradually until, at the end of February, he expectorated about one-half ounce of bright red blood. Thereafter he became very weak with pain in chest, and had to give up work; he was unable to stay in bed because of feeling of pressure and cough, and slept sitting up. There were constant knife-like pains in the left chest, exaggerated by cough and deep respiration; also anorexia and marked dyspnœa on exertion.

*Physical Examination:* The thorax was well developed and there was slight retraction of both clavicular fossæ. The apex beat of the heart was heard in the fifth space; there were no murmurs or thrills; the left border was not definable; pulses equal; arteries sclerotic. The lungs showed limited expansion on the left side; the left lung was flat throughout, no breath sounds or râles. The right lung was resonant; the inspiration exaggerated, and there were fine râles posteriorly during inspiration and large and fine râles anteriorly. Physical examination was otherwise negative. On May 10th, it was noticed that the veins of the upper part of the chest and neck were dilated; there were also marked cyanosis and dyspnœa.

Fluoroscopic examination showed the left side to be dense; there were mottled areas and extension of infiltration on the right side; the surface of the lung was extremely hard and nodular, and suggested a new growth. X-ray diagnosis: New growth.

The urine was negative; blood count showed white blood cells 13,000; differential count: polymorphonuclears 78 per cent., transitionals 11 per cent., eosinophiles 1 per cent., lymphocytes 5 per cent., large mononuclears 5 per cent.; sputum negative for tubercle bacilli on fourteen different occasions. The temperature varied between 100 and 101 and at one time rose to 102° F.; pulse 78 to 104; respiration 20 to 32. The patient lost nine pounds during his stay in the hospital (150 to 141 pounds). The Wassermann test was negative.

*Autopsy:* On opening the left pleural cavity, a large amount of dark, viscid fluid escaped. The lung was soft and densely adherent to the pericardium and to the chest wall. The organ could not be separated as a whole, but had to be torn from the chest wall and mediastinum in shreds. The lung was collapsed, soft, and everywhere contained nodules which varied in size from that of a small pea to about half the size of a hen's egg. The rest of the lung tissue was soft and pulpy, and there was very little evidence of air-containing tissue. The left bronchus contained two small nodules about the size of a pea, which extended into the lung. In the apex of the upper lobe there was an encapsulated mass, about 5 cm. in diameter, from which creamy pus was expressed. The walls of this abscess were made up of white, friable tissue. There was no evidence of other abscesses. The right lung was free in the pleural cavity, without adhesions, and was readily removed. On section, the greater part of the lung was air-containing, but throughout there were small, hard nodules

which varied in size from that of a pea to about half the size of a hen's egg. The intervening lung tissue was dark red in color but crepitant. The right bronchus showed no evidence of infiltration. The pleural cavity contained no fluid and no adhesions.

*Anatomical Diagnosis:* Lungs—carcinoma; chronic fibrinous pleuritis; atelectasis; abscess; acute bronchitis; carcinoma of bronchus (left).

*Microscopic Examination:* Microscopically the lungs showed large, pale staining cells, with prominent nuclei, appearing in cords or strands, and occupying the lung alveoli. There was but little of a connective tissue framework present. The nodules in the right lung were similar to those in the left. Microscopic diagnosis: Carcinoma arising from mucous glands of left bronchus.

*Case 4.* Adult male, fifty-one years of age, married, American, admitted to Bellevue Hospital September 9, 1920, died September 14, 1920. The patient stated that he had been engaged in newspaper work since he was twenty-one years of age; he smoked a moderate amount of cigarettes and took alcohol occasionally; he had measles and diphtheria during childhood; wife and one child alive and well.

The onset of the patient's illness occurred in February with grippe, at which time he was confined to his bed for one week. Since then, he suffered from cough, dyspnœa, pain in chest, chills, fever, and night sweats; lost weight and strength; moderate expectoration, anorexia, no hemoptysis.

*Physical Examination:* The patient appeared to be well developed and well nourished, but chronically ill. The lungs showed very little expansion on the right side; posteriorly vocal fremitus was absent from the midscapular region to the base; there was flatness over the same area and no breath sounds; above this area there was harsh breathing with few râles. Respirations were impaired at the apex on the left side and there were compensatory breath sounds throughout the left lung. The liver was palpable and there was a mass in the lower hypochondriac region, firm and slightly nodular, moving on respiration. Twelve hundred c.c. of blood-tinged fluid were removed from the right side on September 10, and 300 c.c. of similar fluid were removed from the left side on September 11.

X-ray examination showed the right chest to be apparently full of fluid; the left chest showed two rounded areas of consolidation; diagnosis, metastatic lung tumor. X-ray of the kidney showed nothing abnormal. On the day before death occurred, the patient became very weak, the pulse rapid and the temperature subnormal.

The sputum was negative for tubercle bacilli on three examinations. The pulse varied between 120 and 130; temperature 97° to 98° F.; respirations 24 to 34. The urine showed a trace of albumin and granular casts; Wassermann reaction negative.

*Diagnosis:* Carcinoma of stomach with metastases in lungs; tuberculosis; effusion on right side.

*Autopsy:* On opening the chest, the pericardium was pushed over to the left of the mid-sternal line. The right pleural cavity was filled with a sero-sanguinous fluid which had pushed the right lung (atelectatic)

into the cardio-hepatic angle. The excessive amount of fluid explained the descent of the diaphragm.

The left lung was removed easily, and was about normal in size. At the apex, however, there was a large, firm nodule, about the size of a plum. In the center of the upper lobe was a smaller nodule about the size of a walnut. The rest of the upper lobe was crepitant. In the lower lobe there was a hard nodule, about the size of a plum, but the rest of the lung was crepitant. On section, these nodules were composed of whitish, somewhat soft tissue, and had an irregular outline. The pleura was smooth and glistening.

The right lung was small and pushed into the cardio-hepatic angle. Only the periphery of the organ was crepitant and seemingly not involved. The inner half was made up of new growth. The mediastinal lymph nodes were involved and appeared as large, white conglomerate masses. These lymph nodes were so intimately associated with the tumor growth of the lung that lymph nodes and lung had to be removed en masse. The right pleural cavity contained about two quarts of sero-sanguinous fluid. The pleura was studded with cluster-like white growths, most marked on the lateral and diaphragmatic surfaces. The bronchus on the right side was thickened, white and of a fibro-cartilaginous consistence, and merged with the lymph nodes and extended into the lung.

The right kidney was of normal shape and size. The capsule stripped easily and exposed a smooth surface. Differentiation between cortex and medulla was well shown. The substance of the kidney was firm to the touch. The left kidney was about twice the normal size and to it was attached a large amount of fatty tissue. On section, the cut surface showed the medulla to be replaced by a mass of yellowish-white, soft material. The growth had infiltrated the upper pole, but in the lower part there was a zone of intact cortex. The capsule was so intimately attached to the growth that it was difficult to distinguish it and to peel it off.

*Anatomical Diagnosis:* Carcinoma of right lung with metastases in mediastinal lymph nodes, pleura, and left lung; atelectasis (right); hydrothorax (right); apical adhesions of left lung; metastatic carcinoma of left kidney.

*Microscopic Examination:* Microscopically, the lung tumor was similar in appearance to the one described in the last case. The kidney metastases in their morphology were similar to those of the lung. Microscopic diagnosis: Carcinoma arising from mucous glands of right bronchus.

*Case 5.* Adult male, thirty-eight years of age, Irish, married, electrician by occupation. Family history: father died as the result of an accident, mother of old age, one brother died of pneumonia and one sister during childbirth; one sister living. The patient stated that he drank tea and smoked tobacco excessively, but had not taken alcohol in eight years; he had gonorrhœa twenty years ago. His illness began on November 19, 1919, with cough and pain in right chest and thick yellowish expectoration. In December of the same year the sputum became streaked with blood; the expectoration was greatest in the morning. The patient lost considerable

weight (dropped from 175 to 145 pounds in four and a half months) and became pale.

*Physical Examination:* There was marked dullness over the upper third of the right chest anteriorly and from the apex to the spine of the scapula posteriorly. The chest was asymmetrical and there was diminished expansion of the right side. The percussion note was dull over the upper part of the right chest, and extending down to the second rib and behind to the spine of the scapula. The breathing was high pitched over this area and many coarse and fine dry râles were heard. The heart was situated in the third space, extending two and three-quarter inches to the right and two and one-half inches to the left. Fluoroscopic examination showed almost complete consolidation of upper half of right upper lobe, with a cavity about the size of a small onion situated anteriorly, about opposite the third rib, this cavity being partly filled by fluid. No physical signs of a cavity could be made out. The patient expectorated about four ounces of sputum per day. These symptoms continued, the patient losing weight rapidly. He had three severe attacks of pulmonary hemorrhage, succumbing to the last attack quite suddenly on October 8, 1920.

The sputum was examined fourteen times for tubercle bacilli with negative results. The urine showed a faint trace of albumin and an occasional granular cast. Blood count showed white blood cells 19,200; polymorphonuclears 82 per cent., transitionals 1 per cent., lymphocytes 14 per cent., eosinophiles 3 per cent. The temperature was 102° F. on admission, but remained normal during his stay in the hospital. The Wassermann reaction was negative on two occasions.

The patient was first seen in December, 1919, when fluoroscopic examination showed a small dense shadow at the hilus of the right lung, about 1.5 cm. in width by 4 or 5 cm. in length. Subsequent frequent fluoroscopic examinations showed this shadow to expand and cover the upper lobe as a more or less concentric mass, the shadow becoming darker as time went on.

*Autopsy:* On opening the chest, the left pleural cavity was normal. The right pleural cavity was almost completely obliterated by fibrous adhesions which were markedly firm and almost stony hard in the region of the upper lobe in the posterior portion. The thymus was replaced by fat.

The left lung in the gross was normal. The right lung was removed with difficulty and its surface was covered by fibrous bands. Along the upper lobe it had become a dense, white, almost calcific blanket. On section of the lung, two abscess cavities were found, one in the upper lobe, the other in the lower lobe. Both these abscess cavities measured, roughly, 8 to 10 cm. in diameter, though the one in the upper lobe was larger than that in the lower lobe. Both cavities contained a mass of blood clot. The cavity in the upper lobe situated near the lower margin was lined with a whitish flake-like substance, friable and easily removed. There was no firm delineating membrane surrounding either cavity. The remainder of the upper lobe was hard. On section, it was of a grayish, opaque appearance, and through it radiated massive streaks of fibrous tissue arising from a

dense white structure at the hilus This firm mass was found connected with the primary upper right bronchus from which it apparently took origin. The bronchus was completely surrounded by tumor tissue and finally merged with it. The abscess in the lower lobe was situated near the upper portion and, except for blood clot, it contained nothing worthy of record. There was, however, very little odor to the organ. The lower portion of the lobe was slightly congested. The middle lobe was somewhat compressed and firmly bound to the upper and lower lobes by dense adhesions. The branches of the bronchi contained blood clot and were streaked with blood. Hemmorrhagic foci in the abscesses could not be determined.

*Anatomical Diagnosis:* Epithelioma of lung and bronchus (right); abscesses of lung (secondary); chronic interstitial pneumonia; chronic adhesive pleuritis; pulmonary osteo-arthropathy.

*Microscopic Examination:* Microscopic sections taken from several areas of the lung and bronchus showed a very cellular, squamous cell tumor in which there were typical pearl formations. Microscopic diagnosis: Epithelioma of right lung arising from the right bronchus.

W. G. MacCallum (*Text-Book of Pathology*, p. 961) refers to a series of primary lung tumors, among which were several instances of a large cavity in the lung, lined by opaque, yellowish-white, friable, crumbling tissue, in some of which the bronchus could be traced directly into the cavity, its wall becoming thickened by a new growth of the mucosa, which became continuous with the margins of the lining of the cavity. Microscopically, the tumor was made up of strands of atypical stratified epithelium, showing all the characteristics of cutaneous cancers. MacCallum believes it may be an example of metaplasia, but also suggests that it may be dependent upon an embryonic displacement of cells destined to become squamous epithelium. These tumors seem to be in accordance with the one which we encountered.

*Case 6.* Adult male, forty-one years of age, married, a packer by occupation, admitted to Bellevue Hospital April 3, 1920, died June 18, 1920. The patient's father died at the age of sixty, cause unknown; mother died at fifty-five of stomach trouble; two sisters died at the ages of twenty-seven and twenty-nine, respectively, cause unknown. Previous history—the patient had had measles, pertussus, bronchitis, scarlatina; in adult life, recurrent bronchitis; operative—circumcision and varicocele; had gonorrhœa at the age of twenty, no lues. Habits: drank coffee, tea, whiskey and beer; bowels regular; nocturia for past three or four years.

The onset of his illness occurred in December, 1919, with pain in the right chest posteriorly, in the scapular region; was strapped by a doctor and told to go back to work. Two weeks later, he stopped work again and rested for three weeks on account of pain in chest, fever, and cough with expectoration. His sputum was examined on three occasions and found negative for tubercle bacilli. At the end of three weeks, he felt better and returned to work for two days, when symptoms recurred, and then he noticed swelling of the veins of the neck. He went to a hospital, remained there forty-seven days, and was then referred to Memorial Hospital for treatment of tumor of chest. X-ray at the first hospital was negative for new growth. Dyspnœa became gradually marked, also headaches, vertigo with coughing and numbness and tingling in left arm after violent coughing. He lost about twenty pounds in weight in four months.

*Physical Examination:* There was no cyanosis or dyspnœa in the recumbent position. The veins of the neck, back and arm were dilated and prominent. There was no limitation of expansion of the lungs and tactile fremitus was diminished at the right base posteriorly and laterally. There was flatness over the same area, and harsh vesicular breathing at the right apex posteriorly, just above the area of flatness. The breath sounds were broncho-vesicular, almost bronchial, and were absent at the base. Normal vesicular sounds were heard over the left chest. Heart—apex beat not visible; faintly palpable with point of maximum intensity in the fifth space, three and three-quarter inches from mid-sternal line; no thrills; no enlargement by percussion; no murmurs; pulses regular. The abdomen was negative on external examination. The axillary and right cervical lymph nodes were palpable. On May 20, 100 c.c. of clear straw-colored fluid were removed from the right chest; on June 6, 125 c.c. were aspirated and on June 17, 625 c.c. of reddish clear fluid were removed (sp. gr. 1.018, much fibrin). On May 27, right hemiparesis was noted, also slight motor aphasia. On June 15, the patient became drowsy, but was still rational, with frequent hiccough.

Three X-rays were taken; the first showed pleural effusion (4/9/20); the second, interlobar abscess between right upper and middle lobes, effusion in right costo-phrenic space (5/17/20); the third, new growth of lung with pleural effusion, no metastasis in bony skull.

The urine was negative; Wassermann reaction on blood and spinal fluid negative; colloidal gold reaction on spinal fluid negative. The temperature varied between 99.8° and 102° F., averaging about 101°; respirations 18 to 32; pulse 88 to 120.

On June 18, the patient died.

*Autopsy:* The right pleural cavity was distended by pale brownish-colored fluid in the form of pockets. The right lung was everywhere firm to the touch and it was chiefly adherent over the sides. The costal pleura was thickened and on the pleura near the sixth and seventh ribs there was a firm tumor mass, whitish in color, measuring about one inch in diameter. The right bronchus was everywhere infiltrated with firm, white tumor

growth. The upper lobe was bluish red in color and presented a number of what appeared to be abscesses of smaller size. The lower lobe contained in its center a considerable amount of softened, whitish material, resembling the appearances of a lung undergoing resolution. The left lung showed compensatory emphysema and the upper lobe was large and extended somewhat over the middle line. Section presented no other appearances than that of congestion; the bronchi were normal in appearance except for congestion of the mucous membrane.

*Anatomical Diagnosis:* Primary tumor of right bronchus with metastases in right cerebellar lobe and right kidney.

*Microscopic Examination:* Microscopically, the tumor, as well as its metastases, presented large, clear, pale staining cells, similar to those found in the above described bronchial growths. Microscopic diagnosis: Carcinoma of right bronchus.

*Case 7.* The patient was a woman sixty-six years of age, who was admitted to Bellevue Hospital February 9, 1921, and died February 27, 1921. She stated that she had lost considerable weight during the past year (exact amount not known); appetite was poor, and bowels constipated. She also stated that she had been operated on for cystocele (date not given). The onset of her illness occurred four weeks previous to admission to the hospital, characterized by pain in the left side of the chest, with coughing and gradual loss of strength and weight. Associated with this condition she developed edema of the lower extremities with some arthritis of the left hip; she expectorated small amounts of dark rusty sputum.

*Physical Examination:* Revealed an elderly female, weighing about 110 pounds, poorly developed and nourished. The skin was dry and scaly; no palpable adenopathies; marked anæmia. The pupils reacted to light and accommodation. The patient held her head forward as though too weak to support it and there seemed to be some separation between the seventh cervical and first dorsal vertebræ. The thorax was poorly developed and no apex beat was visible. There was some dullness with increased breath sounds over the left upper lobe and crepitant râles over the right middle lobe anteriorly and in the left axilla in the fifth and sixth interspaces. The heart was not enlarged; there were no murmurs; the sounds were distant and of poor quality and the vessels sclerosed. The liver was felt two fingers' breadths below the costal margin; the spleen and kidneys were not palpable. There were no varicosities or ulcers of the lower extremities; the knee jerks were normal; no Babinski or Oppenheim. On February 10, many crepitant and subcrepitant râles were noted, with dullness and distant bronchial breathing over the left infraclavicular region, and on February 26, there was consolidation of the left lobe.

The urine was amber-colored, sp. gr. 1.010, reaction acid, albumin faint trace, glucose negative, granular casts, few red blood cells. Blood count: Leucocytes 6,800, number of cells counted 50, polymorphonuclears 70 per cent., transitionals 3 per cent., lymphocytes 27 per cent. The Wassermann reaction was negative; the sputum was negative for tuberculosis. The temperature was 101.6° F. on admission and varied between 98.4° and 103.4°. The pulse varied between 110 and 140.

*Clinical Diagnosis:* Chronic interstitial pneumonia.

*Autopsy:* On opening the chest, the precordial area appeared normal in size, the right border being overlapped by the edge of the right lung. The right pleural cavity had scattered strands of loose fibrous adhesions over it. The left pleural cavity had many easily broken down adhesions extending over the upper lobe. Both cavities were dry.

The lungs did not collapse completely when removed. The surface of both lungs presented a lobulated appearance. Smoothly rounded lobules, 1 to 3 cm. in diameter, were marked off by deep fissures so that the appearance was similar to that of a hobnailed liver with very large knobs. This lobulation extended throughout practically the whole of both lungs, but was less marked at the extreme base. The lungs were heavy and felt moderately firm, except for the extreme right base and the lower third of the left lobe. Each individual lobule had superficially the light cottony feeling of the emphysematous lung, but on deeper pressure, firmer tissue was felt. The surface was light gray and mottled with anthracotic pigment. The pleura, except in the fissures described, had a smooth glistening appearance but not on the right diaphragmatic surface, and between the right middle and lower lobes. Here it had lost its luster and there was an adherent exudate of greenish fibrin. On section, the lung presented a dirty gray appearance, imperfectly aerated, and a number of dilated spaces containing greenish-yellow pus. These were lined by a definite membrane, and one or two admitted a probe for some distance, suggesting that they were bronchiectatic. The smaller bronchi exuded pus on pressure.

The liver was normal in size. The capsule was thin and tense and somewhat adherent to the diaphragm and transverse colon. One fibrous nodule, about 0.5 cm. in diameter, was visible beneath the capsule on the anterior surface. On section, it cut with resistance and extended into the liver tissue.

*Anatomical Diagnosis:* Right lung: organizing pneumonia; adenocarcinoma; acute fibrinous pleuritis; bronchiectasis; emphysema; purulent bronchitis. Left lung: fibrinous pleuritis; interlobar empyema; purulent bronchitis; bronchiectasis; emphysema; organizing pneumonia; adenocarcinoma. Liver: corset liver; metastatic nodule (adenocarcinoma); perihepatitis.

*Microscopic Examination:* Sections from the lung showed a fibrous tissue hyperplasia in places, together with many areas of prominently defined epithelial growths scattered throughout both lungs. Microscopic diagnosis: Carcinoma arising from the finer bronchioles in the lung.

The diagnosis of primary lung tumors presents one of the most interesting as well as one of the most difficult problems in clinical medicine. The possibility of metastases from a symptomless growth in an esophageal diverticulum or a small growth in the gall-bladder, thyroid, etc., is always well worth considering.

No positive diagnostic criteria are known. Frequent examinations with the fluoroscope are most apt to reveal a progressive growth.

*Discussion:*

DR. LARKIN: It is difficult to discuss primary tumors of the lung. One of the present specimens is a large tumor centrally located which has all of the characteristics of tumors which are primary in the bronchi. The other specimen seems not to be connected with the lung, but is a tumor which is invading the lung secondarily and is primarily a pleural neoplasm. It has that very peculiar character of incrusting the pleura, sending ramifications into the lung and along the bronchi. These tumors are interesting, not only because of their pathological rarity, but also because of the clinical phenomena during the life of the patient. I have in my collection six or eight tumors like the specimens shown here, and the more I have studied the histology of the type of tissue in order to arrive at a conclusion as to where the tumor originated, the more I am bewildered. The tumor, with the incrustation, seems to me to be a tumor primary in the pleura, for it has the physical characters of ramifications and the incrustation of the pleura and the involvement of the bronchi. These tumors may be diagnosticated from physical evidence during the life of the patient, for they are usually accompanied by large amounts of pleural exudate, generally hemorrhagic in type. A number of years ago Dr. Ewing made a diagnosis of primary endothelioma of the pleura from a centrifugalized exudate. Only recently I have seen a case in which a large amount of hemorrhagic fluid was withdrawn from the pleura and on examination of the centrifuged sediment there was no question of the diagnosis of endothelioma. At autopsy a tumor of the right lung was found, which is exactly similar to the specimen shown here to-night.

DR. MOSCHCOWITZ: I do not think the diagnosis of primary tumors of the lung is quite as difficult as Dr. St. George makes it out. The majority of tumors of the lung seem to be of three types: first, those that resemble mediastinal tumors, and I think these are mostly primary tumors at the hilus of the lung arising from the bronchus. I should like to call attention to an early and characteristic sign, and that is the fixation of the trachea. It has very little lateral and vertical mobility. The second form in which tumors of the lung may present themselves clinically is that where you find a solid mass situated in one or the other lung. The third type simulates pleurisy with effusion and this is the one which I think offers the most difficult problem in diagnosis. I find that you can often make a diagnosis much better by taking the centrifugalized fluid, fixing it in formalin so that it comes out a gelatinous mass from the bottom of the test tube, and running it through paraffine. The chances of finding tumor cells are far better than by simply making a smear.

DR. EWING: This winter I have seen at autopsy two cases of epithelioma of the lung arising on tuberculous bronchitis—highly malignant squamous

carcinomas. The proportion of cases Dr. St. George found free from tuberculous lesions is unusual. I wonder whether he has thoroughly searched the tissues for tuberculous lesions.

DR. LARKIN: Do I understand Dr. Ewing to say that there is a connection between tuberculosis of the peribronchial tissues and the malignant growths?

DR. EWING: In these cases there were active tuberculous lesions in the lungs from which the epithelioma developed.

DR. LARKIN: Were the tumors of any great size?

DR. EWING: No.

DR. LARKIN: Was the diagnosis macroscopical or microscopical?

DR. EWING: Both.

DR. ST. GEORGE: In answer to Dr. Ewing's question as to whether we searched the tissues for tuberculosis, we did. The only one that showed any evidence of tuberculosis was the sarcoma case and that had some nodules at the apex.

As regards the diagnosis of these tumors, I do not want to convey the impression that it is so exceedingly difficult, although to differentiate a primary lung tumor from a metastasis is difficult to some extent. Recently at a meeting here in New York a clinician said he had diagnosed thirty lung tumor cases, but all without an autopsy; hence whether they were correct diagnoses is a debatable question. We have presented only those cases of primary lung tumor which can be proved beyond doubt to be so. Dr. Norrie has seen a number of these cases at the hospital and even in the patient where the shadow was observed growing from the lung he was not willing to make a diagnosis of tumor, but held to his diagnosis of abscess. He would not say whether they were primary lung tumors, or were metastatic. In the autopsy service at Bellevue the percentage of tumors metastasizing into the lung is rather large, and we hesitate to make a diagnosis of primary lung tumor.

I do not know which specimen Dr. Larkin referred to as being an endothelioma, but I believe it is the one which I had seen six weeks after onset of symptoms and which showed the shadow at the hilus. I knew the man very well and followed him up. In another hospital they had made a diagnosis of tuberculosis in his case, largely I believe because they obtained a ++++ tuberculous complement fixation. I had him fluoroscoped repeatedly during the following months, and we found the shadow to grow out and into the lung. I think it is fair to assume that it is a bronchial growth. Some of the sections are suggestive of the tumor starting from the glands of the bronchus.

# THREE BRAIN TUMORS

NATHANIEL B. STANTON, M.D.

(*From the Laboratory of the Lenox Hill Hospital, New York City*)

In his text-book on Neoplastic Diseases, Ewing states that probably one per cent. of all deaths are due to brain tumor, while Tooth in an analysis of 632 cases gives as the relative frequency in location: tumors of the brain proper 94 per cent., of the pituitary 2 per cent., and of the pineal gland less than one half of one per cent. Based on an analysis of 434 cases, the frequency of various histological types is tubercle 183, gumma 45, sarcoma 113, glioma 127, osteoma 4, and cholesteoma 2.

The cases recorded in the present report are of the pituitary and pineal glands. Of the various histological types encountered in the pituitary gland the order of frequency is diffuse hyperplasia with focal adenoma, adenocarcinoma, and last sarcoma. An analysis of sixty-eight cases of pineal tumor gives as the most common types in the order of frequency: cysts either with or without tumor growth, teratomata, and finally ependymal glioma.

The general symptomatology of cerebral neoplasms may be considered under three headings: (*a*) symptoms common to all tumors, such as headache and evidence of increased intracranial pressure; (*b*) localizing symptoms, such as paralysis; (*c*) symptoms due to disturbance of special function associated with neoplasms of the pituitary and pineal glands.

The special symptoms arising from neoplasms in the pituitary may be divided into two groups: (1) the cephalic type, in which pressure symptoms are predominant; (2) the dystrophic type, in which disturbances of growth are prominent symptoms. In the cephalic type the chief complaints are headaches, dizziness and paralyses, or interference with other portions of the visual apparatus. The dystrophic type may again be divided into four groups: giantism with or without acromegaly, infantilism, acromegaly, and that condition spoken of as adiposis genitalis.

The tumors of the pineal gland show as endocrine disturbances: hypertrophy of the sexual organs, overgrowth of the pubic hair, and precocious sexual instinct.

The first case, that of a pituitary carcinoma, has the following history. A male, age sixty-two years, complained of severe pains in the abdomen lasting for the past six weeks. This pain was continuous, burning in nature and did not radiate; it was made worse by eating and was not relieved by vomiting. There was no hematemesis. There were also present a slight cough and considerable loss of weight. He had had severe headaches and a ptosis of the right eye for three weeks, and a ptosis of the left eye for a short time about five weeks previous to admission.

Physical examination showed the following pathological conditions: emaciation; the right pupil dilated, irregular and sluggish in reaction; a divergent squint; diplopia; and atrophy of the optic nerves. During his illness all ocular nerves except the external rectus of the left eye became paralyzed. There was a palpable tumor mass in the left upper quadrant of the abdomen. The abdominal and cremasteric reflexes were absent and there were shooting pains in both legs.

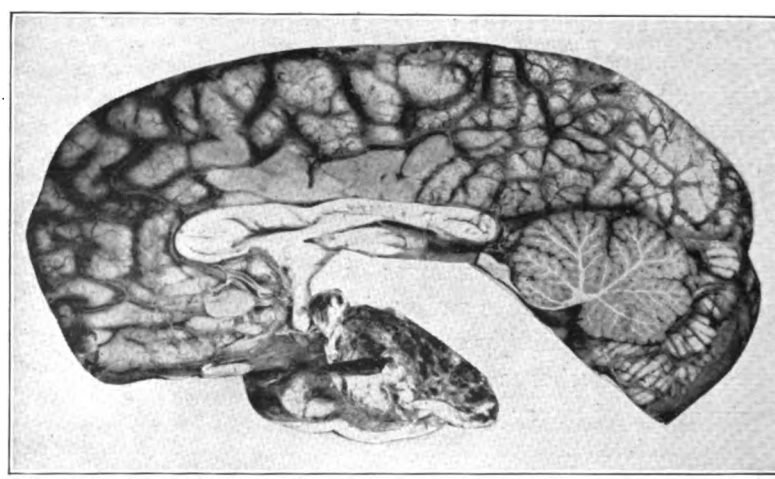


FIG. 1.

X-ray examination showed erosion of the sella turcica and destruction of the clinoid processes, and in addition a large, dense, irregular consolidation at the root of the right lung which increased in size very rapidly as shown by later pictures. Further radiographic examination showed a constant deformity in the prepyloric region of the greater curvature of the stomach. Gastric analysis showed an absence of free hydrochloric acid and a total acidity of nine. The blood sugar was 81 milligrams per 100 c.c.

The unusual features found at autopsy were several. At the hilus of the right lung there was an irregular neoplasm which involved the large vessels and the main bronchi and which measured 13 cm. in the greatest

diameter. The central portions of the growth were necrotic. All of the mediastinal nodes were involved in a neoplastic process and matted together the lungs and heart. The head and the larger portion of the body of the pancreas were replaced by neoplastic tissue. There were several metastases in the mesentery and omentum, the largest measuring 8 cm. in diameter. In the mucosa of the stomach at the greater curvature near the pylorus, there were three metastases, the largest of which was a sessile mass 3 cm. in diameter. Both adrenals showed metastatic deposits and there were growths in the spleen and in one kidney, as well as several neoplastic deposits in the skin and subcutaneous tissue.

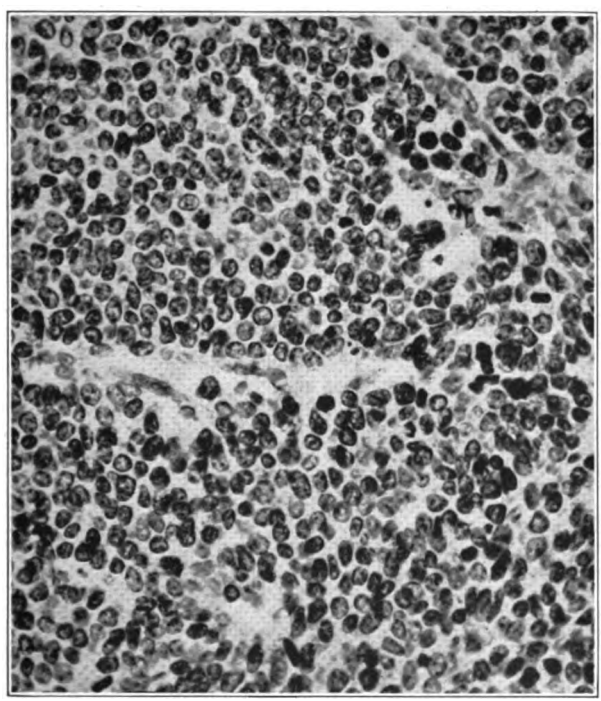


FIG. 2.

The convolutions of both hemispheres of the brain were markedly flattened and the pia arachnoid showed a marked edema. In the region of the pituitary gland there was a soft mushy neoplasm which had very extensively eroded the sella turcica, and which was tightly adherent to the bone and meninges and which by direct extension had invaded the optic commissure. Both lateral ventricles were much distended and contained excessive amounts of fluid. In the position of the third ventricle (Fig. 1) there was a dark, red, smooth, globular mass, 4 cm. in its greatest diameter and which had a sessile base. Section through the mass showed that the base extended through the brain and was continuous with the neoplasm involving the pituitary gland.

Microscopic examination showed the tumor to be a small cell epithelial neoplasm (Fig. 2) whose architecture, particularly in the primary growth in the pituitary, was that of a papillary form, the cells being about a center core consisting of a thin-walled blood vessel supported by a loose connective tissue. Areas of necrosis were relatively common. In sections through the pituitary the gradual transformation from the normal cells of the pars anterior to frankly malignant cells was demonstrable.

The interesting phases of the case were the absence of evidence of disturbed endocrine function, the widespread metastasis, and the absence of disturbances in sugar metabolism as evidenced by a normal blood sugar and absence of sugar in the urine, this in spite of widespread lesions, which involved pancreas, adrenals and pituitary.

The second case of pituitary tumor, also a carcinoma, occurred in a male aged eighteen years. He was admitted to the hospital because of persistent headaches, gradually developing blindness and paralysis of the third and ocular branch of the fifth nerves on the right side. There was somnolence and loss of weight. The X-ray examination showed no erosion of the sella turcica. The evidences of disturbed endocrine function were emaciation, absence of axillary hair, poorly developed genitalia, a fine smooth skin and the general appearance of a youth about five years younger than his given age.

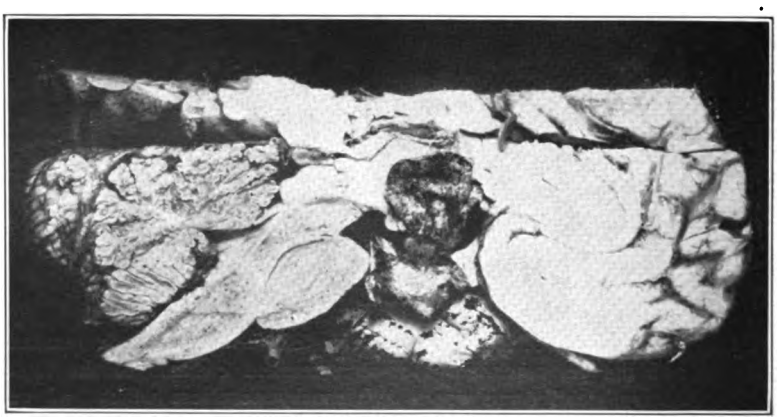


FIG. 3.

Upon opening the skull a large amount of clear cerebro-spinal fluid escaped. The convolutions of the right forebrain were found to be markedly flattened. The pituitary was replaced by a soft hemorrhagic mass which had almost completely destroyed the clinoid process of the right side and had eroded the saddle of the sella turcica so that there was an opening into the sphenoidal cells (Fig. 3). The mass was tightly adherent to the me-

ninges and measured 2.5 x 1.75 cm. Both lungs showed small hemorrhagic infarcts. The testes were atrophic. The other organs were of no particular interest.

The microscopic examination of the second tumor showed a carcinoma of the alveolar type (Fig. 4) though the individual cells were of the same

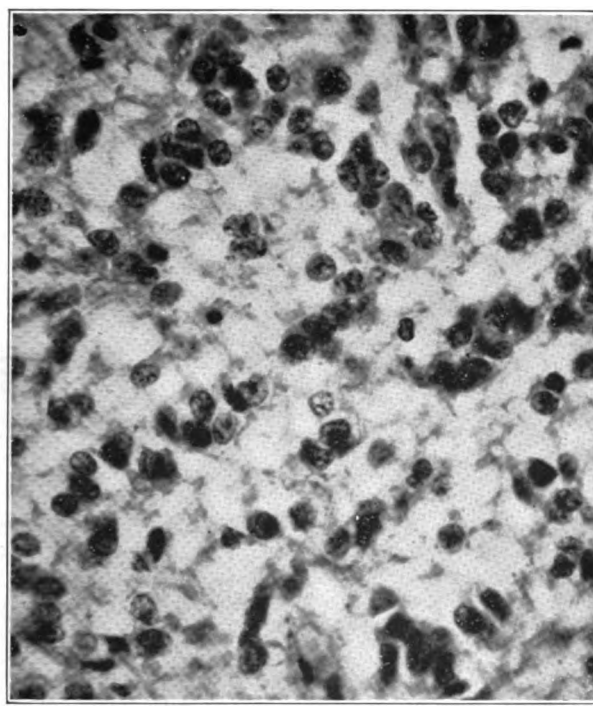


FIG. 4.

general character as the first tumor described. The alveoli were of varying size and while in some areas definite lumina were demonstrable, in others cellular proliferation had filled the lumina. There were extensive areas of hemorrhage and smaller areas of degeneration.

In marked contrast to the first case, the second instance showed no metastasis and gave evidence of endocrine disturbance.

The third case of this series was a multiple cyst of the pineal gland discovered accidentally at autopsy and giving rise to no symptoms during life. A male, twenty-six years of age, complained of pain in the back of the neck and shortness of breath for five weeks. The pains were throbbing, radiated to the occipital region and kept him awake at night. At the same time there were stinging pains in the fingers and toes which lasted from

a few hours to a few days. There was no evidence of endocrine disturbance in either history or physical examination.

Physical examination showed a heart enlarged downward and to the left; a double mitral murmur at the apex and a diastolic murmur at the aortic area transmitted to the vessels of the neck. There were petechiæ in the conjunctivæ and skin and a blood culture showed *streptococcus viridans*. During his stay in the hospital he ran a septic temperature.

At autopsy the clinical diagnosis of malignant endocarditis was confirmed. The present interest is in the brain which was normal except for a small tumor of the pineal gland, 1.5 cm. in diameter (Fig. 5).

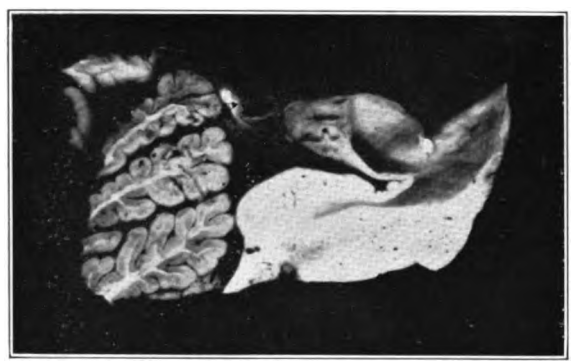


FIG. 5.

Microscopical examination of the pineal growth showed a somewhat distorted and persistent pineal gland with foci of calcification and larger and smaller cyst cavities either lined directly by the normal pineal cells, or lined by a moderately thick layer of glia tissue.

The three cases have been presented not so much for their relative rarity, but as illustrations of the extensive neoplastic destruction which on occasion may occur in one of the endocrines without giving rise to the conditions usually associated with endocrine dysfunction.

*Discussion:*

DR. EWING: I would like to ask what was the structure of the abdominal and other metastases in the second case. It is very rare to have so many metastases from pituitary tumors.

DR. ROHDENBURG: The morphology of the metastases was the same as that of the original tumor. Metastases were present in practically every organ of the body.

DR. EWING: Was the structure of the pituitary tumor characteristic of any you have seen before in the pituitary?

DR. ROHDENBURG: The morphology of the primary tumor was typical of other pituitary tumors which I have seen.

# FIBRO–SARCOMA OF THE APPENDIX

G. L. ROHDENBURG, M.D.

*(From the Pathological Laboratory, Lenox Hill Hospital, New York City)*

While epithelial neoplasms of the appendix, even though they are seldom clinically malignant, are not infrequent, neoplasms arising in the other types of tissue present in the organ are relatively rare. If chronic irritation is the important factor in tumor genesis, as is currently supposed, it would not be at all strange to see malignant change in the organ, for in relatively few individuals is there absence of evidence of chronic inflammation. Possibly the apparent rarity of clinically malignant tumors in this situation may be explained by the fact that in the vast majority of cases the chronic inflammation becomes acute and the offending focus is removed, either before the cancer age or before the irritation has persisted for a sufficiently long period.

The present case is that of a male, aged seventeen years, admitted to the hospital on the service of Dr. George Semken. His family history was strongly tubercular, and the patient himself stated that three months before admission he suffered from a cough, was feverish, and had profuse night sweats. With the exception of his cough the symptoms remained and two weeks before admission he noticed a mass in the region of the appendix. The only clinical and laboratory data of positive nature were the presence of a rounded mass, freely movable, in the region of the appendix, a septic type of temperature, and a radiographic finding that the tumor was attached to the cæcum. Tuberculosis could not be demonstrated either radiographically in the lungs or by various laboratory examinations. At a laparotomy a rounded, reddish tumor was found attached to the cæcum where the base of the appendix should have been, the omentum being attached to the edge of the tumor. The growth was extremely vascular, receiving its chief nutrition from the omental attachment.

The tumor measured 13 x 10 x 12 cm. and, as previously stated, attached to one surface was a broad band of omentum containing many large-sized blood vessels. At the other pole projected the lumen of the appendix which was patent throughout.

Microscopically the tumor was found to be composed largely of small spindle-shaped cells embedded in a fibrillar matrix (Fig. 1), which was scanty or fairly abundant and richly infiltrated with small round cells.

Spindle cells were fairly numerous and were spread diffusely throughout the tumor or arranged in parallel or interlacing bundles. Among these

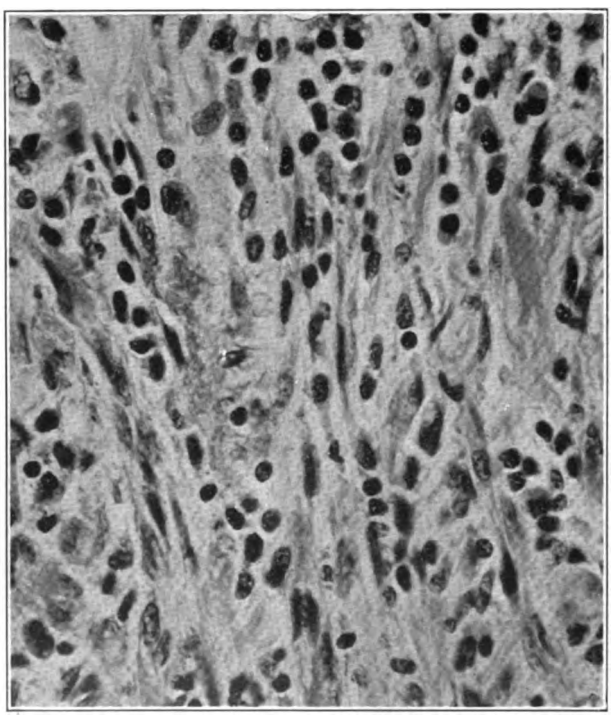


FIG. 1.

cells were a few larger cells of round or spindle shape with hyperchromatic nuclei and acidophile protoplasm. The tumor contained many small blood vessels and capillaries.

The case is interesting from the standpoint of diagnosis, for with a familial history of tuberculosis, an onset of distinctly tubercular type and a mass in the iliocæcal region, the differential diagnosis between iliocæcal tuberculosis and neoplasm was not easy.

# A TUMOR OF THE LEFT AURICLE

P. D. HOFFMAN, M.D.

*(From the Pathological Laboratories, Bellevue and Allied Hospitals, Dr. Douglas Symmers, Director, New York)*

The rare incidence of primary tumors of the heart is illustrated by the fact that in 3,000 autopsies at Nüremberg, Thorel did not encounter a single one; the Bellevue Hospital records of over 7,000 autopsies include no cases.

One of the first collections of primary tumors of the heart was made by Berthenson, who, in 1893, reported 28 cases of the following varieties: sarcoma 9, myxoma 7, fibroma 6, carcinoma 3, lipoma 2, cyst 1. As to location, 7 were in the right auricle, 3 in the right ventricle, 7 in the left auricle, 5 in the left ventricle, and 4 in the septum.

Link, in 1909, collected 91 cases; on some of them, however, the data were scanty, so that all may not be authentic. Myxomata and sarcomata are the most frequent cases in his series. In addition to this series, 11 cases of rhabdomyoma were collected by Wolbach in 1907.

Karrenstein's collection, in 1908, included 39 cases, excluding myxoma, and 38 cases of myxoma. This collection is of interest in regard to the location of the tumors. He finds that in the case of myxomata the left auricle is the most frequent site, while out of 6 cases of sarcoma 5 were located in the right side of the heart.

According to recent literature, the myxoma is the tumor of far the most frequent occurrence. A case of this tumor was reported before this Society by Louria in 1917. Thorel believes many of these reported as myxomata are in reality thrombi that have undergone myxomatous degeneration. He likewise rejects many reports of fibroma as being organized thrombi.

The first case of primary sarcoma was reported in 1865 by Bodenheimer. This case had been observed clinically and brings up the interesting question of the diagnosis of cardiac tumors.

No cardiac neoplasm has thus far been diagnosed during life. The diagnosis in this case most nearly approached a correct one. It was: "Cardiac disease of unknown origin."

The reason for the difficulty in diagnosis lies in the fact that there are no symptoms characteristic of cardiac tumors, but these resemble the symptoms of any form of cardiac disease and their character depends upon the size and location of the tumor. It has frequently been observed that there may be no symptoms referable to the heart, and the condition is discovered unexpectedly at autopsy. A number of writers have cited symptoms which they believe should be suggestive of a tumor of the heart. Thus Fraenkel considered bloody pericardial effusion, in the absence of tuberculous or scorbutic disease, a certain sign of cardiac neoplasm. This has, however, not been observed in any cases other than his own. Berthenson (1893) lays emphasis on embolic manifestations, but others consider these unusual in cardiac neoplasms. He also discusses murmurs, which may or may not be heard, and which, if present, may not be so clear as in endocarditis and may vary in intensity. Others mention exclusive involvement of one side of the heart.

The case to be presented tonight is as follows:

H. F., a male, thirty-seven years old, was operated on at Bellevue Hospital for inguinal hernia on January 18, 1921. He had never had symptoms referable to the heart and had an entirely negative medical history. On questioning, after cardiac signs were discovered, he said he had had rheumatism in the wrists several years ago. Examination of the heart showed enlargement to the left and rough apical presystolic and diastolic murmurs were heard. Compensation was so good that general anæsthesia was not contraindicated. The patient was discharged February 12, cured of the hernia, and was referred to the cardiac clinic. After he left the hospital, his feet became swollen and he was somewhat dyspnœic. He came to the cardiac clinic and was referred to the ward on March 15. The patient became rapidly more dyspnœic and cyanosis appeared. The respirations were 40. There was ascites, tympanites and edema of the feet and legs. Leucocytosis and fever were present.

Physical examination showed a well-developed man, dyspnœic but lying flat in bed. Examination of the heart showed moderate enlargement to the right and left, with the apex beat in the fifth interspace outside the midclavicular line. The heart sounds were of fair muscular quality, irregularly irregular, rate 140. A systolic murmur was heard at the apex and a diastolic

murmur at the base and in the aortic area. The diagnosis was (1) chronic cardio-valvular disease with mitral stenosis and insufficiency and relative aortic insufficiency, (2) cardiac hypertrophy and dilatation, (3) au-

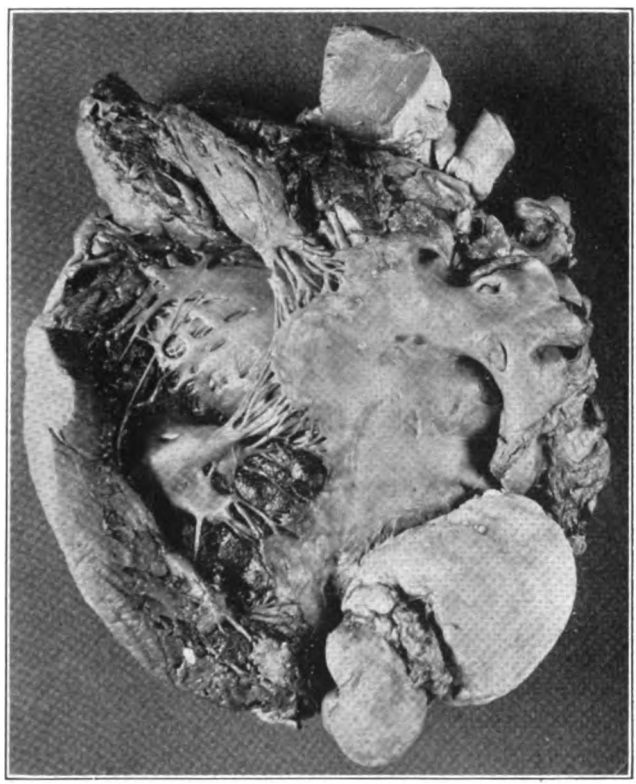


FIG. 1.

ricular fibrillation, (4) congestion, bases of both lungs, (5) chronic passive congestion of the liver, (6) coronary sclerosis and thrombosis with myocarditis, (7) ascites.

The morning after admission, at about eleven o'clock, the patient went into shock. The extremities were cold and blue, with drenching perspiration. The temperature was elevated; the pulse was not palpable at the wrist, and respirations were rapid and labored. The patient died suddenly, growing very blue just before death. The first heart sound was of good force and muscular quality within ten minutes before his sudden death.

The autopsy was performed a few hours after death. The main anatomical diagnoses were as follows: Tumor of left auricle, verrucous endo-

carditis of mitral valve, cardiac hypertrophy and dilatation, chronic fibrinous adhesive pleuritis, chronic passive congestion of the liver, fibroma of the left suprarenal gland, ascites, edema of lower extremities.

The pericardium was normal and contained no excess of fluid. The heart was moderately enlarged, especially the right ventricle. The right auriculo-ventricular orifice admitted three fingers easily. On exploring the left auriculo-ventricular orifice, it was found to admit only one finger, and a smooth, rounded body, slightly movable, was felt at the side of the orifice. On opening the heart, the valves of the right side and the aortic valves were found to be normal and there was no change in the endocardium. There was slight thickening of the walls of the right ventricle and dilatation of both ventricles. There were no changes in the coronary arteries. The mitral valve showed some thickening of the posterior cusp and of the attached chordæ tendineæ. The anterior cusp showed numerous small, somewhat flat, reddish, verrucous growths.

Attached to the antero-lateral wall of the left auricle was a firm, whitish mass, the size of a hen's egg. This was attached to the auricular wall for all except the lower 2 cm. of its length. The whole mass was 7.5 cm. long and 5 cm. wide at its widest part, which was about the middle. It was irregular in contour, smooth, but not glistening. The endocardium appeared to extend for about 4 mm. up the side of the mass. The lowest portion, which had no direct attachment to the auricular wall, projected into the auriculo-ventricular opening and was the rounded body felt on exploring the orifice before the heart was opened. It could be rotated slightly and in the formalin-hardened specimen is to be seen displaced upward and laterally. There was a band of rough reddish material, apparently fresh thrombotic deposit, separating the lower portion from the main body of the growth.

The mass was considered as probably a thrombus, with the possibility of its being a tumor.

Microscopic examination of sections removed from the mass in the left auricle revealed the fact that it was divisible into three zones. The lowermost zone was composed of apparently well-preserved heart muscle, superimposed upon which and constituting a second zone was a layer of fibrous tissue. The third zone presented a rather complex histology. Just above the connective tissue septum were masses of spindle-shaped cells which were arranged in whorls or bundles and which were indistinguishable from smooth muscle cells. These gradually faded into areas where all normal cell relationships were lost, the cells being irregular in arrangement and variable in size, provided with very little intercellular substance, the nuclei more or less richly chromatic, in places hyperchromatic, the whole representing, apparently, sarcomatous transformation of the supporting connective tissue. In some of the sections cells of this general type were found scattered around slit-like formations representing, possibly, dilated capillary vessels. In one of the sections, also, was a small collection of cartilage cells, some of which were evidently undergoing calcification. The presence of cartilage cells suggests the possibility that the tumor is teratomatous in nature.

Moreover, it is difficult to account for the presence in the growth of smooth muscle cells except on a developmental basis, unless one assumes, of course, that they are derived from the muscular layer of the nutrient arteries of the heart.

As stated above, the first case of primary sarcoma of the heart was reported in 1865. In 1910 Baldwin collected seventeen cases which he considered authentic, including one of his own. In 1918 Perlstein reported a case of sarcoma apparently originating from the epicardial areolar tissue. He had made a careful search of the literature, and enumerated thirty cases beside his own, omitting all those whose true sarcomatous nature appeared to him to be doubtful.

There are three interesting points in connection with the present case:

1. It illustrates the difficulty in distinguishing between a thrombus and a cardiac tumor without careful microscopic examination. The appearance of the tumor is that of a thrombus and, indeed, it consists in large part of thrombus which has been deposited on the tumor.

2. The location in the left atrium is unusual in this type of tumor. In Perlstein's thirty cases eleven were situated in the right atrium. The septal wall of the atrium is also a much more frequent site of attachment than the antero-lateral wall, which was the attachment in the present case. The septal wall is considered as having a disposition to tumor formation, perhaps from the complicated foldings and displacements which take place in development at this place (Marchand and Fuhrman).

3. The fact that the tumor projected through the mitral orifice, partially occluding it and giving rise to symptoms of mitral stenosis, is of great clinical interest. Link gives fourteen cases of cardiac tumor in which the mitral orifice was thus obstructed. In one case death was thought to be due to incarceration of the tumor in the orifice. Considering the sudden death, with extreme cyanosis just before death, such a mechanical factor may have been responsible in the present instance. Symptoms of both mitral stenosis and insufficiency were given by most of these tumors, and these were present in this case.

A case of this sort on which there was extensive clinical observation was reported by Pavlowsky in 1893. One of the most interesting facts in connection with this case was the observation that when the patient was lying down the signs were those of mitral insufficiency, while when she was examined sitting up signs of mitral stenosis were found. The patient could hardly be persuaded to assume a sitting position and was evidently in much greater distress than when lying down. At autopsy a tumor of the left auricle was found which, in the vertical position, would occlude the mitral orifice, giving rise to serious stenosis, and in the horizontal position would recede slightly, relieving the stenosis, but interfering with closure of the mitral flaps, thus causing insufficiency.

*Bibliography*

1. THOREL: *Ergeb. d. allg. Pathologie u. Pathologische Anatomie,* 1903, ix, 901; 1907, xi, 443; 1915, xvii, 677.
2. BERTHENSON: *Virchow's Archiv,* 1893, cxxxii, 390.
3. LINK: *Ztschr. f. klin. Med.,* 1909, lxvii, 272.
4. KARRENSTEIN: *Virchow's Archiv,* 1908, cxciv, 127.
5. LOURIA: *Proc. N. Y. Path. Soc.,* 1917, xvii, 85.
6. BALDWIN, H. A.: *Jour. Am. Med. Assn.,* 1910, lv, 646.
7. PERLSTEIN: *Amer. Jour. Med. Sci.,* 1918, clvi, 214.
8. PAVLOWSKY: *Berlin. klin. Wchnschr.,* 1895, xxxii, 393.

*Discussion:*

DR. PAPPENHEIMER: I should like to ask whether the smooth muscle fibers which normally are found beneath the endocardium might not be a theoretical source of origin for the muscle fibers which enter into the composition of the tumor; also whether the auricular muscle had been invaded by the growth.

DR. HOFFMAN: No; there was a band of connective tissue between the muscle wall and the tumor.

DR. EWING: I would like to know what the histological diagnosis in this case is.

DR. HOFFMAN: It is sarcoma of the left auricle.

DR. SYMMERS: In view of the fact that cartilage and smooth muscle cells are present, one must consider the possibility that the tumor is a teratoma. But, as Dr. Pappenheimer has already suggested, it is likewise possible that the smooth muscle tissue represents a normal structure. It seems to me that the more probable diagnosis is that of sarcomatous transformation of the connective tissue stroma of a fibromyoma.

DR. EWING: It is much more cellular than any of the tumors of this

sort that I have ever seen, and I think on that account it is a very important case, because it gives a much better opportunity to determine the nature of these tumors than we ordinarily have. Most of them are very edematous so that the original structure is obscured. Here we have a well-nourished, large, solid tumor, from which I think it ought to be possible to come to some definite histogenetic diagnosis. My single glance at the specimen suggests two possibilities which I hesitate to mention after such a brief study—myosarcoma or neurogenic sarcoma. It might be worth while to try to demonstrate neuroglia fibrils by special stains.

DR. HOFFMAN: I ought to mention that probably the largest bulk of the tumor is composed of thrombus, so it may really be a small tumor with large deposits of fibrin.

## TWO CASES OF CONGENITAL LESIONS OF THE HEART

ALEXANDER FRASER, M.D.

These cases, though showing a number of developmental defects, are primarily and essentially extremely rare forms of stenosis of the aorta. Stenosis of the aorta, as compared with that of the pulmonary artery, is rather rare, the relation being about that of one to four, and of extreme forms like those about to be presented I have been able to find a record of only three or four in the literature. Aortic stenoses are classified by Herxheimer (Schwalbe's Handbuch) as follows: (1) Those involving the conus up to the valves; (2) those occurring in the region of the ductus arteriosus; (3) general hypoplasia of the aorta.

These two cases illustrate extreme degrees of classes one and two respectively.

*Case 1.* This heart was taken from a well-developed and nourished male child aged five days, born of apparently healthy parents. On the afternoon of the fifth day, he became diffusely cyanotic, developed convulsions and died suddenly. Apart from the heart, the viscera were well developed and showed no evidence of disease other than passive congestion. The heart at first sight appeared to be a three-chambered organ, consisting of two auricles and one ventricle (the right), but on further dissection I found the following: (1) a large right auricle with normal entrance of the venæ cavæ, patent coronary sinus and foramen ovale; (2) a large right ventricle with thick walls and distended chamber occupying

two-thirds of the interior of the organ, normal tricuspid and pulmonary valves, large conus and main artery which after giving off the right and left pulmonary branches is continued as the ductus which arches downwards to form the descending aorta; (3) from about the middle of the arch of the ductus a branch about half its size is given off to the right and this in turn gives off the left subclavian, carotid, and innominate above while it sends a small branch, 1 to 2 mm. in diameter, downwards to the right of and behind the pulmonary artery where it terminates in the right and left coronary arteries with normal branching and distribution; (4) the left

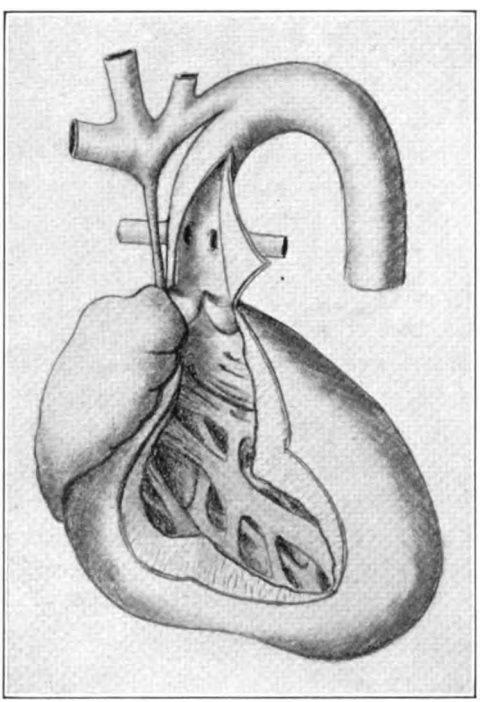


FIG. 1. Drawing of heart in case 1. Right ventricle and pulmonary artery opened.

auricle receives the pulmonary veins normally. It is about one-third the size of the right. The foramen ovale is patent. The mitral valve is represented by a tense sheet of endocardium without chordæ tendineæ or papillary muscles. Beneath this is a small endocardial-lined, blind pocket about 3 x 5 mm., representing the left ventricle from which there is no outlet.

This is a case of atresia of the whole left conus up to the aortic valves with resulting non-development and atrophy of the

left ventricle and of the ascending aorta, the only function of the latter being to supply the coronary arteries with blood received through the ductus arteriosus.

*Case 2.* This case also was that of a male child that died on the fifth day, having lived exactly one hundred and twenty hours. He was well developed and nourished, and the history of the parents, as far as could be ascertained, was negative. On the afternoon of the third day while nursing he became suddenly dyspnœic, the respirations becoming very rapid and shallow. After this the whole surface of the body showed a dusky brown mottling. The temperature was 100.4. The urine showed albumin and a few pus cells. On the fourth day the dyspnœa and cyanosis

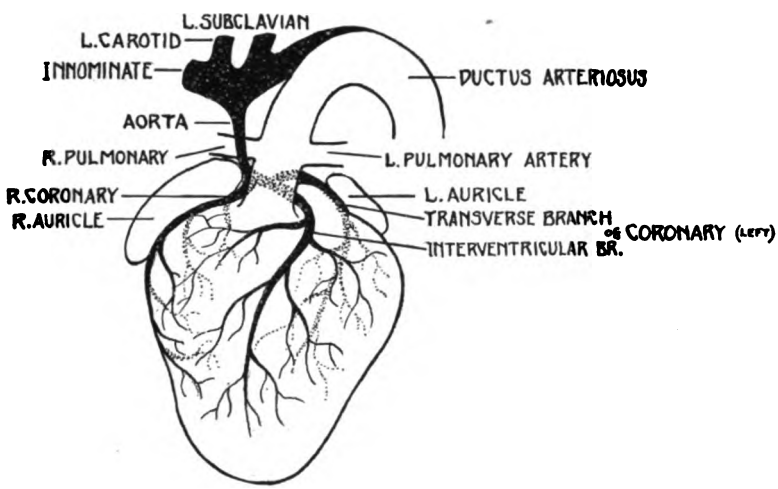



FIG. 2. Semi-diagrammatic drawing showing coronary arteries branching from the atrophic ascending aorta.

were more pronounced. The capillary circulation of the finger tips was good and recessive on inspiration. Systolic murmurs were heard over the whole cardiac area but were not transmitted to the axilla or vessels of the neck. In the right infrascapular region was an area of dulness with increased voice sounds. On the sixth day the child died and the body was sectioned. All the tissues showed passive congestion and considerable edema. The lungs showed atelectasis, congestion, edema and some patches of pneumonia. The description of the heart is as follows: (1) The right auricle is quite large with the openings of the cavæ and coronary sinus in normal position. The septum ovale (primum) is absent, leaving a large irregular opening between the two auricles. (2) The right ventricle has a large chamber and thick walls (nearly twice as large as the left). The tricuspid valve is defective, irregularly formed and has vegetations on

the cusps. The conus is large and points upwards to the right instead of to the left. There is a triangular-shaped opening about 10 x 7 x 7 mm. in the bulbar region of the interventricular septum (Kieth's Bulbar Defect). The cusps of the pulmonary valve are covered with low vegetations. The pulmonary artery is large and lies slightly behind and well to the right of the aorta. After the right and left pulmonary branches are given off, the ductus arteriosus arches up and then turns downward to form the descending aorta. The only communication between the ductus and aorta is a small

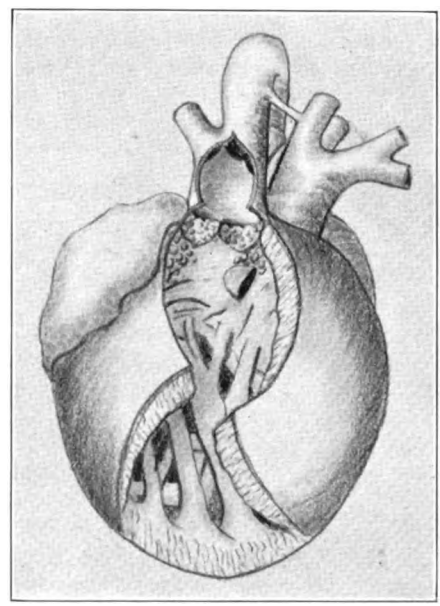


FIG. 3. Drawing of heart in case 2, showing right ventricle and pulmonary artery open, patent interventricular septum, vegetations on valves, atresic isthmus.

fibrous thread, one mm. in diameter, extending between its outer surface and that of the left carotid, which represents the obliterated isthmic portion of the aorta. (3) The left auricle and ventricle are only about half the size of the right chambers, the ventricle being in front of and twisted around the left ventricle as the latter is twisted around it normally. The mitral valve is deformed by fibrous adhesions and vegetations. The aortic valve is normal. The aorta emerges to the left and in front of the pulmonary artery and terminates in the innominate, left carotid and left subclavian branches. In short the left heart supplies the upper, while the right supplies the lower part of the body.

This is an extreme form of the second class of aortic stenoses,

namely, stenosis—in this case atresia—in the isthmus or ductus region. There are two well-recognized forms of constriction in this region: (1) the fetal type, in which the stenosis is so great that the ductus must remain patent in order that life may continue; (2) the adult type, in which the constriction is not so great as to necessitate continued patency of the ductus. In this case it usually closes after birth. Later in life the constriction increases and necessitates the development of anastamoses between branches arising above and below the stenosis (internal mammaries, epigastric, scapular, intercostals, etc.).

*Discussion:*

DR. NORRIS: I should like to ask in the first case of congenital heart disease whether there was any transposition of viscera or any other anomaly.

DR. FRASER: No. There were no other anomalies in either case. They were both well-developed children.

---

## TYPHOID LESIONS OF THE KIDNEY

ALEXANDER FRASER, M.D.

The lesion of the kidney usually found in typhoid fever consists of the degenerative changes common to all acute infections, or occasionally of embolic abscesses due to secondary infection. As far as I am aware, the specific typhoid lesion has not been described. Osler in his text-book on medicine mentions, without giving references, that Rayer, Wagner and others had encountered "small lymphomata which later may go on to suppuration," but evidently neither he nor they interpreted these as a specific reaction to the typhoid bacillus. Mallory, to whom I had shown sections of the cases about to be described, told me that he had seen an occasional small focus of endothelial leucocytic reaction, but never lesions so extensive or so typically developed as in this case.

The patient, a young sailor twenty-three years old at the time of his admission to St. Vincent's Hospital, had been ill eight days with a very

toxic acute infection. He had roseolæ, some of which were hemorrhagic, a well-marked leucopenia with relative lymphocytosis, and gave several positive Widal reactions. The urine contained numerous cells which were interpreted as pus cells, but which judging from the results of an examination of the urine found in the bladder at autopsy I am satisfied were mononuclear phagocytes with ingested lymphocytes. The autopsy, which was performed about fourteen days from the onset of the first symptoms noticed, showed numerous typical typhoid lesions, mostly "cribriform" ulcers in the

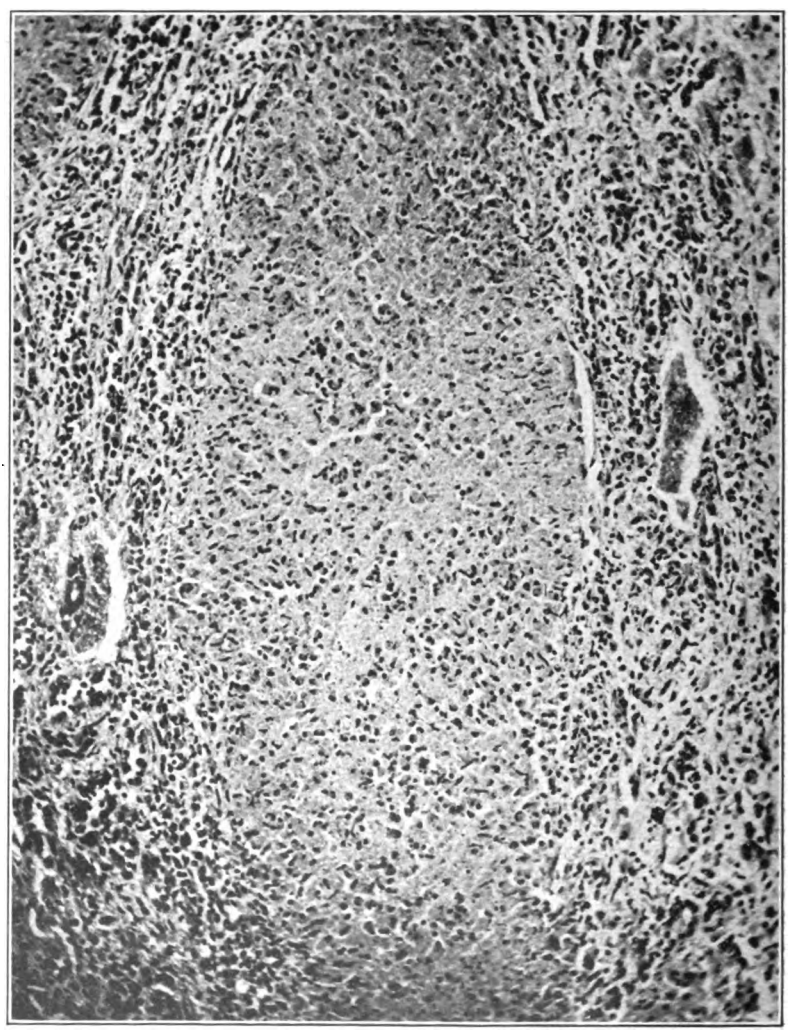


FIG. 1. Low power microphotograph showing typhoid lesion with central necrosis.

ileum and cæcum together with greatly enlarged, congested and occasionally hemorrhagic mesenteric lymph nodes. Microscopic examination confirmed the presence of true typhoid lesions in the intestine, lymph nodes, spleen and bone marrow, but not in the liver. The kidneys presented a remarkable picture. They were both large and diffusely congested with numerous yellowish-white, elevated, rounded or oval areas with deep red borders scattered over the whole surface. Section showed these spots penetrating the whole of

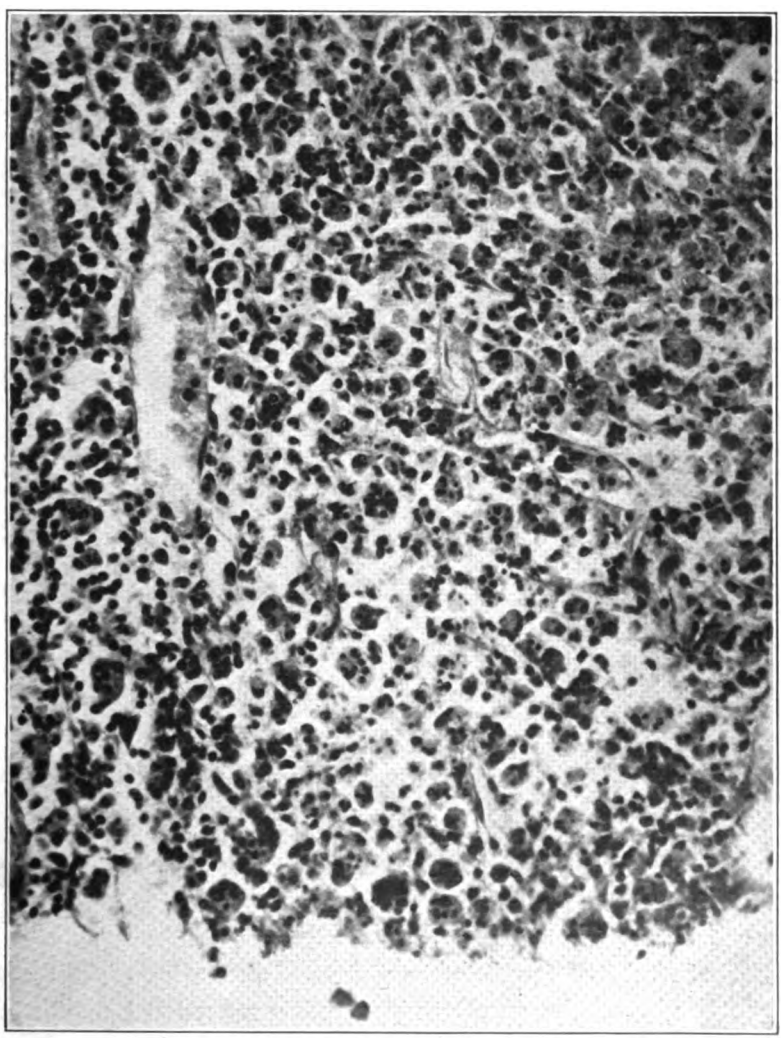


FIG. 2. High power microphotograph showing mononuclear phagocytes with ingested lymphocytes.

the parenchyma of both organs, presenting in the pyramids as long yellow streaks, extending over the pelvis and mucosal surface of the ureters and spreading out over the mucosa of the bladder. To the naked eye the picture suggested staphylococcus embolic abscesses, but microscopic examination showed no polymorphonuclear leucocytes. The lesions consist of round, or elongated oval collections of large mononuclear phagocytes with extensive central necrosis (Fig. 1.) The well-preserved peripheral parts consist of a fair number of lymphocytes but mostly of large phagocytes containing lymphocytes and occasionally red blood cells in their cytoplasm, many of them showing ten to fifteen cells at a single focus (Fig. 2).

Such cases must be exceedingly rare or they have been overlooked in the routine examination of typhoid patients and interpreted as cases of secondary embolic abscesses. Histological examination of six museum specimens labeled "embolic nephritis" reveals one case exactly like this. So, too, examination of large numbers of sections from kidneys in typhoid fever, showing nothing macroscopically, convinces me that small isolated foci of true typhoid reaction are not at all infrequent. It is not improbable, too, that more careful microscopic examination of the urine in typhoid would show that not infrequently the "pus" cells found are mononuclears with ingested lymphocytes. A quick way of settling the question would be the use of the oxydase reaction.

## HYPERPLASIA OF THE PARATHYROID GLANDS IN RICKETS

JOHN MINOR, M.D., AND A. M. PAPPENHEIMER, M.D.

*(From the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York City)*

Of late years considerable attention has been directed to structural changes in the parathyroid glands associated with diseases in which there is a disturbance of calcium metabolism.

Erdheim[1] had found in the rickets of rats a hyperplasia and hypertrophy of the parathyroid glands proportional to the intensity and the duration of rickets in the animals. He found

also more numerous mitoses in the glands from rachitic than in those from normal animals. Although the reasons for these parathyroid changes are still to be explained, Erdheim regarded them as secondary to the rachitic lesions and not as the cause of them. In the parathyroids from human cases Erdheim was unable to differentiate histologically glands from rachitic and non-rachitic children.

Ritter[2] has recently studied the parathyroids from ten rachitic and fifteen non-rachitic children. None of his non-rachitic cases, however, fell within the usual age limits for the occurrence of rickets in children. He found that while in non-rachitic children in the first year the parathyroids consisted predominantly of clear cells belonging to the so-called Type I, in rachitic children they consisted almost entirely of dark smaller cells belonging to Type II, usually showed a marked increase in fibrous tissue, and marked hyperemia and edema. He also concluded from his study that no influence of the general state of nutrition of the child upon the histology of the parathyroid could be recognized.

The present study was made on the parathyroid glands of fourteen rachitic and eighteen non-rachitic children—routine autopsy material from the Nursery and Child's Hospital. Twenty-two separate glands were studied in the rachitic, nineteen in the non-rachitic cases.

In order to gain a general idea of the comparative size of glands from rachitic and non-rachitic infants, the sections were outlined at a constant magnification by the use of a projection apparatus. Allowing even for the gross inaccuracies of a method depending on the size of sections not known to be through the plane of greatest diameter of the gland, the area of the sections from the rachitic cases in almost every instance surpasses, and often greatly surpasses, that of the sections from the non-rachitic. Translated into volume, this certainly indicates a great excess of glandular tissue in the rachitic cases.

Our next problem then was to determine whether this increase in size were due to increase in the size of the individual cells, or to the multiplication of cells, or to some other factor. Choosing

five glands from the rachitic and five from the non-rachitic series, from children of approximately the same age, careful measurements were made with the micrometer eye-piece of fifty cells and nuclei from each gland. The cells were chosen at random from all portions of the glands, only making sure to choose those as symmetrical in shape as possible. The results are shown in the table:

| | Case No. | Age in Months | Nutrition | Cell Diameter in $\mu$ | Nucleus Diameter in $\mu$ |
|---|---|---|---|---|---|
| Non-rachitic..... | 289 | 3 | Poor | 7.76 | 5.21 |
| | 299 | 6 | Good | 7.30 | 5.87 |
| | 325 | 9½ | Fair | 10.16 | 5.13 |
| | 329 | 9½ | Good | 10.20 | 5.83 |
| | 321(II) | 12 | Fair | 7.14 | 5.39 |
| Rachitic..... | 361 | 5 | Emaciated | 10.09 | 5.24 |
| | 333(II) | 8 | Good | 8.41 | 5.26 |
| | 334 | 9 | Emaciated | 7.51 | 5.10 |
| | 375 | 10 | Good | 9.30 | 4.92 |
| | 335 | 12 | Good | 10.31 | 6.23 |

It will be seen that there was found no constant difference in the size of either cells or nuclei in rachitic as contrasted with non-rachitic cases. Neither was there shown any constant relation of the size of cell or nucleus to the nutritional state of the child. Since the histologic study showed no increase in connective tissue, no edema and no difference in vascularity or congestion, we felt justified in concluding that the increase in size of the glands in rachitic cases is due to multiplication of cells.

A brief résumé of the histology of the parathyroid gland is as follows: There are three general types of cell arrangement—in compact masses, as cords of cells separated by blood vessels and connective tissue septa, and a less frequent form showing a lobular structure. There are also three types of cell found: I, clear, vegetable-like cells with unstained cytoplasm, large vesicular nuclei and clear cell outlines; II, rose-red cells with finely granular cytoplasm, small dark nuclei and indefinite cell outlines; III, Welch's oxyphile cells, which last are rarely found before the tenth year.

Comparative histologic study of the twenty-two glands from rachitic and nineteen from non-rachitic cases revealed no constant differentiating features. There was an increase in connective tissue in the glands in only one rachitic case, and this increase was only slight. There was no greater vascularity or congestion in rachitic than in non-rachitic cases, and no evidences of edema were found.

In all our sections, the clear cell belonging to Type I predominated markedly, and as constantly in rachitic as in non-rachitic cases. The other cells present belonged to Type II and showed no constant arrangement with regard to blood vessels. No mitoses were found; this, however, could easily be due to lateness of fixation.

Our conclusions from this study, then, are:

1. That there is a very definite increase in the size of the parathyroid gland in cases of human rickets, and that this increase in size is due to multiplication of cells, not to an hypertrophy of individual cells or increase in supporting structures.

2. That the parathyroid glands in children within the first eighteen months of life consist predominantly of clear cells belonging to Type I.

3. That in human rickets there is no constant or characteristic change in the cell type, and the clear cells still remain markedly predominant.

4. That in our cases there was no increase in supporting tissues in the parathyroid gland in rickets, and no increase in vascular supply, or evidence of congestion not found equally in non-rachitic cases.

5. That the state of nutrition of the child had no bearing on the size either of the gland as a whole or of the individual elements.

*References*

1. ERDHEIM: Rachitis und Epithelkörperchen Math.-Naturwiss. Kl. d. Kais. Akad. d. Wiss., 1914, xv.

2. RITTER, CARL: Ueber Epithelkörperchenbefunde bei Rachitis und andere Knochenerkrankungen, *Frankfurter Ztschr. f. Path.*, 1920, xxiv, no. 1.

*Discussion:*

DR. JOBLING: Definite conclusions cannot be drawn from this study by Drs. Minor and Pappenheimer, as the glands were not weighed and measured at the time they were removed, but the results are very suggestive.

DR. PAPPENHEIMER: There is an apparent paradox in the relation of the parathyroids to calcification, which has not been explained. It is generally known from the work of Erdheim and Toyofuko that complete destruction of the parathyroid in rats is followed by a failure of the dentine to take up calcium and also by a lack of calcium deposition in the callus of experimentally produced fractures. Identical changes, as regards the failure of calcium deposition, occur in rickets, but associated with a hyperplasia of the parathyroid. One can of course theorize about the explanation of this seeming discrepancy, but there is as yet no real explanation.

# PRIMARY BONE TUMORS

## THEIR CLASSIFICATION WITH SPECIAL REFERENCE TO BENIGN GIANT-CELL TUMOR

H. S. MARTLAND, M.D.

*(From the Pathological Department of the City Hospital, Newark, N. J.)*

For a number of years I have noted a considerable confusion and lack of clear thought among surgeons and pathologists as regards the diagnosis, treatment and prognosis of the primary tumors of the long pipe bones belonging to the so-called sarcoma group.

It is rather unfortunate that even at the present time many able and even noted surgeons are extensively sacrificing limbs for tumors which have been known to be distinctly benign in character.

It is for this reason that I will attempt to summarize some of my experiences encountered in this type of tumors. I have tried to do this in as practical a way as possible, consequently much scientific data will obviously escape recognition in this discussion.

The primary mesenchymal tumors of bone may be roughly classified as follows:

TABLE I

CLASSIFICATION OF PRIMARY TUMORS OF BONE

*Primary Mesenchymal Tumors of Bone*

FIBROBLASTOMA (fibroblast).
*Benign:* Fibroma, and border-line fibrosarcoma (unusual).
*Malignant:* Fibrosarcoma (see osteogenic sarcoma).

MYXOBLASTOMA (myxoblast).
*Benign:* Myxoma, myxofibroma, myxolipoma and myxochondroma.
*Malignant:* Myxosarcoma, myxochondrosarcoma and osteomyxochondroma.

CHONDROBLASTOMA (chondroblast).
*Benign:* Chondroma, ecchondrosis, chondromyxoma and osteochondroma. Multiple congenital enchondromata.
*Malignant:* Chondrosarcoma, osteochondrosarcoma, etc.

OSTEOBLASTOMA (osteoblast).
*Benign:* Osteoma, osteophytes, exostosis, endostosis, osteofibroma, etc.
*Malignant:* Osteogenic sarcoma.

ENDOTHELIOBLASTOMA (blood-vessel endothelioblast).
*Benign:* None.
*Malignant:* Endothelial myelomas and multiple hemangioendothelioma.

MYELOMA (type cell unknown).
*Benign:* None.
*Malignant:* Multiple myeloma (Kahler's disease).

BENIGN GIANT CELL TUMOR.
*Benign:* Single and multiple forms of disease (see ostitis fibrosa).
*Malignant:* None.

If we examine Table I, it will be readily seen that most of the tumors group themselves into benign and malignant forms. Most of the benign forms, though not all of them, can as a rule be easily diagnosed by their history, location, age incidence, clinical appearance and X-ray examination, and therefore offer little confusion either to surgeons or pathologists.

Furthermore, the malignant forms, if studied more in detail, will dwindle down to a few important types. For example, fibrosarcoma would be a rare bone tumor if we interpret tumors belonging to this class as a fibrocellular variety of osteogenic sarcoma. In a like manner, myxosarcoma, myxochondrosarcoma, chondrosarcoma, etc., while they do occur as pure forms which metastasize, are nevertheless most often encountered as metaplastic areas in osteogenic sarcoma.

The confusing primary tumors of the long pipe bones, when

a question of malignancy arises, usually exclude all but the following: osteogenic sarcoma, endothelioma, multiple myeloma and benign giant-cell tumor.

My experience has been that it is impossible, especially in central varieties of these tumors, to diagnose many of them from their age incidence, location of tumor or X-ray examination, but that an exploratory incision with histological examination of the tissue removed is necessary.

## OSTEOGENIC SARCOMA

Of the many anatomical varieties of this tumor described in the literature, for teaching purposes I have adopted the simple classification of Ewing as the best, namely, fibrocellular and chiefly periosteal; telangiectatic, soft and richly permeated with blood-vessels and sinuses (bone aneurysm), involving marrow, shaft and periosteum; and sclerosing, a very hard osteoblastic growth, involving marrow, shaft and periosteum, and to a slight extent less malignant than the other two forms.

It has been found that practically all these growths sooner or later involve the periosteum, making a classification as periosteal sarcoma justifiable in a large majority of the cases. A central sarcoma without involvement of the periosteum I have never seen, and this is interesting, since Bloodgood has recently stated, "I would welcome an opportunity to study a solid central sarcoma in which there is no periosteal growth."

The important facts in osteogenic sarcoma are summarized in Table II.

TABLE II

SUMMARY OF IMPORTANT DATA IN OSTEOGENIC SARCOMA

PATHOLOGY:

| *Anatomical varieties* | *Location* |
|---|---|
| 1. Fibrocellular | Chiefly periosteal |
| 2. Telangiectatic | Marrow, shaft and periosteum |
| 3. Sclerosing | Marrow, shaft and periosteum |
| 4. Capsular | |
| 5. Parosteal | |

HISTOLOGY:
Type cell: spindle, round and tumor giant cells.
Production of new bone.
Hyperchromatic nuclei and tumor mitoses.
CAUSE OF DEATH:
Early lung metastases.
AGE INCIDENCE:
Fifteen to seventy years. Cases few before fifteenth or twentieth year.
TREATMENT:
*Radical Operation* and treatment of any kind almost hopeless. Bloodgood's series showing less than 4 per cent. cures after radical operation and early diagnosis.
*Radium* supposed to be of little or no benefit (see Ewing's discussion).

## ENDOTHELIOMA OF BONE

True primary endothelioma of bone has always been questioned by many pathologists, because of the close histological resemblance of the growth to metastasizing adrenal tumors, tumors of the thyroid, prostate, etc.

I believe that it does occur rather frequently as a single tumor. Rare multiple forms have been described, notably a case of multiple hæmangioendothelioma reported by Symmers, which clinically simulated multiple myeloma.

The importance of this type of bone tumor has recently been emphasized by Ewing, who a few months ago presented to this Society several cases of, I believe, undoubted primary endothelioma of bone, the cases being clear cut enough to form a distinct clinical and pathological entity in bone tumors. This remarkable contribution to the pathology of bone tumors, sharply identifying a type of tumor frequently submerged under the name of round-cell sarcoma, and often mistaken by pathologists for osteogenic sarcoma, is of especial importance, since the malignancy of this tumor is very much less than that of osteogenic sarcoma, persistent X-ray or radium treatment checking and apparently curing the lesion.

TABLE III

SUMMARY OF SALIENT POINTS IN ENDOTHELIOMA OF BONE

PATHOLOGY:
*Anatomical varieties*
1. *Single tumor:*

(*a*) Circumscribed, large bulky growths, arising in marrow or endosteum and early perforating shaft and developing externally.

(*b*) Smaller growths, many occurring in middle of shaft, and submerged in the diagnosis of round-cell sarcoma, periosteal sarcoma, etc. (Ewing's endothelial myeloma).

2. *Multiple Tumors:*

(*a*) Multiple hemangioendothelioma (Symmers), clinically resembling multiple myeloma.

HISTOLOGY:

1. *Single Tumor:*

Type cell is a round or oval-shaped cell with clear cytoplasm and vesicular nucleus. Usually arranged in alveolar formation with little or no intercellular substance. Some portions of the tumor showing origin from blood-vessel endothelium. There is absence of new bone formation, but bone absorption is common.

2. *Multiple Tumors:*

In Symmers's case the histological picture of hemangioendothelioma or angioma was very evident.

CLINICAL COURSE:

The single tumors are not nearly so malignant as osteogenic sarcoma and perhaps amenable to X-ray and radium treatment. Ewing states that tumors rapidly melt under radium but recur unless treatment is persistent.

## MULTIPLE MYELOMA

This is most easily diagnosed by the X-ray examination showing multiple bone tumors, which demonstrates the importance of raying the skeleton in many bone tumor cases. The X-rays being distinguished from multiple metastasizing carcinoma by its predilection for bones with red-marrow and the absence of a moth-eaten appearance.

In a tumor in which the type cell is unknown, and has been described as a myelocyte, lymphocyte, plasmocyte or erythroblast, it is quite possible that with so great a variation in histological structure the explanation may be that we are dealing with an undifferentiated metrocyte, somewhat similar to the explanation suggested by Symmers in the disease "Leukanæmia" (a combination of myelogenous leukæmia and pernicious anæmia).

Multiple myeloma is a rare disease occurring in individuals over thirty-five years of age, oftenest in men, and pursuing a

rapidly fatal course. It is characterized by foci of growth arising in different parts of the marrow system at approximately the same time involving bones with red-marrow, as vertebræ, sternum, ribs, skull, scapulæ and ilium. Spontaneous fractures are common. Bence-Jones albumose is frequently found in the urine.

It occurs in two anatomical varieties, the ordinary form or Kahler's disease in which the lesions are confined to the bones, and a very rare or extra-medullary form in which the lesions may be present in other tissues.

Histologically the type cell has been identified as either unknown, an adult or embryonal myelocyte, a lymphocyte, a plasma cell, or in rare instances as an erythroblast.

Treatment in this disease is of no avail, except mechanical to relieve pressure symptoms.

### BENIGN GIANT-CELL TUMOR

Benign giant-cell tumor, medullary giant-cell sarcoma, giant-cell sarcoma of the epulis type, medullary giant-cell tumor, chronic non-suppurative hemorrhagic osteomyelitis (Barrie), etc., has been recognized for many years by a few surgeons and pathologists as essentially a benign lesion of bone. This fact, however, is unfortunately not appreciated by most surgeons, in spite of all the literature written on the subject.

The tumors usually occur in the ends of the long bones, especially the upper end of the tibia. The majority occur in young people. A definite history of trauma is often obtained and seems to be an important etiological factor in the single lesions. Their growth is slow and duration of disease long. They recur after incomplete removal, *in loco,* but I have never seen one metastasize to distant parts.

X-ray examination shows an expansive, abrupt and circumscribed growth with preservation of the bony shell. Distention may be great.

In gross appearance the tumor is usually confined within the periosteum, definitely circumscribed, not infiltrating, and is easily removed from its bony shell. It is distinctly vascular, simulates

young granulation tissue, is friable, soft, oozes and resembles red-currant jelly or fresh-cut liver.

Histological examination shows a stroma like young granulation tissue, ranging from very cellular, often hemorrhagic, areas to older, non-cellular portions in which the fibroblasts are arranged in whorls and resemble slightly spindle-cell sarcoma. Active mitoses and hyperchromatic nuclei are, however, not present. Giant cells of the foreign body endothelial type with glassy cytoplasm and many (25 to 80) vesicular nuclei are numerous, often forming the predominant picture.

It has been my good fortune to have had under observation with Dr. F. R. Haussling, attending surgeon to the City Hospital, a case of benign giant-cell tumor of the lower end of the tibia for a period of ten years, during which time the lesion has been curetted several times. During this time we have noticed, both from the X-ray examinations, the character of lesion at operation and the histological examination of the tissue, that the lesion has been changing in character from an original solid benign giant-cell tumor to an extensive, localized fibro-cystic disease of the tibia. The lower end of the tibia at the present time shows a very large multilocular cyst of the bone with an old fibrous wall containing only a few giant cells.

I have also had the opportunity of following with Dr. Haussling a very remarkable case of multiple giant-cell tumors for a period of six years. This case I reported before this Society in 1915. At the present time only four well-marked cases of this disease have appeared in American literature.

For several years the tumors in this case which were located in the right superior maxilla, both fibulæ, both clavicles, femurs and ribs were expansive, more or less solid tumors chiefly in the myeloid part of the bones and well confined within their bony shells. They showed the typical histological picture of benign giant-cell tumor.

During the last two years, even in lesions which had not been curetted, these tumors have been becoming cystic along with extensive fibrocystic disease of the surrounding bone. The gross

appearance of one of the lesions at last operation was one of multiple cysts with fibrous walls, showing histologically dense fibroblastic tissue with scant foreign body giant cells.

I do not believe that any single lesion has been under such a long observation, since the tumor is either cured by surgical curettement, etc., or the limb sacrificed by some ill-informed surgeon.

The multiple lesions in their extreme form are so rare that it is doubtful if any case has been observed over such a period of time. The changing in the character of the gross appearance and microscopic picture of the lesions in both the single and multiple case during this time of observation is, in my opinion, extremely interesting.

From my observations in these two cases I am of the opinion that so-called benign giant-cell tumor is entirely an inflammatory process in the nature of exuberant granulation tissue, located mainly in the myeloid part of the bone, formed as an attempt to repair previous bone destruction, due to trauma in the single lesions and in the multiple ones to some unknown cause. I believe the disease is one phase or rather an exaggerated phase of *osteitis fibrosa cystica.*

It is interesting to note that very similar growths are occasionally seen in the tendon sheaths which have microscopic pictures closely resembling these giant-cell tumors of bone, namely, the so-called benign xanthic extra-periosteal tumors of the extremities.

My conception of so-called *osteitis fibrosa cystica* may be roughly summarized in Table IV.

TABLE IV

SUMMARY OF IMPORTANT DATA IN OSTEITIS FIBROSA CYSTICA

NAME OF DISEASE: In my opinion no good, permanent name has been suggested so far. Metaplastic osteomalacia is worth considering.

PATHOLOGY:

*Anatomical varieties*

1. *Localized lesions* (localized osteitis fibrosa cystica).
2. *Generalized lesions* (generalized osteitis fibrosa cystica of von Recklinghausen).

*Location*

Practically always in diaphysis and never invades epiphysis. Slow growth and moves up diaphysis. Most common in proximal end of shaft.

*Etiology*

In single lesion trauma seems to be an important exciting factor. In generalized type of disease the cause is unknown, may be bacterial, nutritional or endocrinal. Usually appears before thirtieth year.

*Sequence of Lesions*

1. Destruction and absorption of bone (usually medullary in cancellous bone).
2. Granulation tissue formed in effort of repair; producing picture of young granulation tissue with hemorrhage, bone absorption and numerous foreign body endothelial giant cells.
3. Replacement by a less cellular fibroblastic tissue, a medullary fibrosis; producing a picture simulating spindle-cell sarcoma.
4. The lesion at this stage may progress in any of the following ways:
   (*a*) Subside, due to softening of fibrous tissue, with formation of single or multiple bone cysts lined by a fibrous wall, the cyst fluid eventually becoming serous and often clear.
   (*b*) Progress as a solid giant-cell tumor with or without cyst formation and finally heal or become bone cyst.
   (*c*) Progress rapidly as a benign solid giant-cell tumor of local clinical malignancy with considerable destruction of bone.

TREATMENT: Radium or surgical curetting with crushing of diseased wall. The success of surgical treatment in our opinion has been due chiefly to *closure without drainage,* thus avoiding sepsis.

## SUMMARY OF CASES REPORTED

CASE 1. Single, solid benign giant-cell tumor of lower end of tibia, changing in a period of ten years into a single multilocular bone cyst.

A. L. Male. Italian. Present age thirty-eight years. Barber.

*Family History:* Negative.

*Past History:* Chancre when eighteen years of age.

*Present History:*

*1907.* Twisted right ankle while playing ball.
In plaster 3 weeks.
Syphilitic treatment for 3 months.
Plaster for 2 months.
Lower end of tibia curetted and discharged cured.

*1908.* Swelling and pain has returned.
Lower end of tibia curetted, diagnosis osteomyelitis.
Sinus persisted.

*1910.* Fell and injured ankle.

Admitted to City Hospital.
Lower end of tibia curetted and diagnosis of solid benign giant-cell tumor made.

*1911.* Tibia curetted 4 times for recurrence.

*1915.* Tibia curetted for recurrence. The original tumor is no longer composed of granulation tissue, but consists of several cystic cavities filled with serous fluid.

*1921.* Patient in good physical condition. Has been able to work as barber all this time. X-ray examination shows a multilocular communicating cyst involving lower third of tibia.

CASE 2. Multiple, solid, expansive benign giant-cell tumors, changing in a period of six years into generalized fibrocystic disease of long bones.

T. K. Female. White. Present age thirty-one years. Married.

*Family History:* Negative.

*Past History:* Venereal diseases denied. Four normal births, one miscarriage.

*1914.* Noticed lump in inner angle of right eye.
Fell and fractured right femur above knee, which united with fair result.
Noticed tumor mass on anterior surface of left tibia.
Admitted to hospital complaining of weakness and pain in bones.
*1st operation:* tibial tumor curetted, microscopical diagnosis benign giant-cell tumor.
*2d operation:* tumors in maxilla, both fibulæ, both clavicles and rib curetted. Gross appearance of tumors that of pale granulation tissue, microscopical diagnosis benign giant-cell tumor.
*3d operation:* right elbow curetted.

*1916.* *4th operation:* left femur curetted.

*1917.* *5th operation:* right tibia curetted.
*6th operation:* clavicle curetted.

*1919.* *7th operation:* both tibiæ and left clavicle curetted.
*8th operation:* left femur curetted.
*9th operation:* finger curetted.

*1920.* *10th operation:* left femur curetted.
*11th operation:* left femur curetted.

*1921.* *12th operation:* left tibia curetted.

At all operations the wound was closed by primary suture without drains, this we regarded as a very important factor in preventing sepsis. The present physical condition of the patient is fair considering her long stay in hospital. She has a moderate secondary anæmia. Her blood chemistry is normal for nitrogenous waste retention, her calcium metabolism, however, has never been determined. The tumor masses in the last few years are distinctly cystic at operation and histological examination shows scant or no giant-cells present but old, dense fibroblastic cyst walls. The indication for operation has been pain. Many of the lesions have disappeared without surgical treatment but the surrounding bone shows extensive fibrocystic disease.

Of the American literature on bone tumors, especially giant-cell tumors, I have been greatly helped in my observations by the numerous writings of Bloodgood, Ewing, Barrie, Symmers and Meyerding.

*Discussion:*

DR. MOSCHCOWITZ: In twenty years' experience I have never seen a patient with a giant-cell sarcoma of the bone come to autopsy. I should like to ask those here if they have had the same experience.

DR. SYMMERS: What part of the bone do you mean?

DR. MOSCHCOWITZ: Any giant-cell sarcoma.

DR. EWING: I think Dr. Martland has given us a great deal of valuable information. I wish he could find time to carry it around to the places where it would do most good. Although the general statements which he mentioned have been known since 1852, the information needs to be spread broadcast in this country. At a recent meeting in this city of prominent surgeons about thirty were present, who were presented with evidence such as has been given to-night of a giant-celled sarcoma in the tibia with all the features and histology described, and they were asked to state what they would do. Twelve of the thirty would amputate. I think this is a deplorable state of affairs when the information is as clear as it is of the benign nature of this disease. The difficulty is not with these characteristic growths in which a large portion of the tumor is made up of giant cells, but in the variants of this disease. I have found quite a few tumors which are in all respects like those described, but in which the giant cells are scattered and the remaining tumor tissue is quite cellular and verging toward the ordinary malignant looking spindle-cell sarcoma. I am unable to come to a conclusion as to whether there are two diseases here which you cannot distinguish histologically and clinically, or by the X-ray, or whether this ordinary simple benign giant-cell tumor may in different cases become a clinically malignant, possibly metastasizing tumor. I am unable to decide what its relations are to the malignant cases of true osteogenic sarcoma. In cutting the capsules of these tumors I find varying degrees of bone formation and bone absorption, and if one sees only small sections, it is very difficult to distinguish the process from malignant osteogenic sarcoma, so I think it is better not to cut into these tumors and attempt to make a diagnosis on a small piece of tissue. One ought to have all the data in the case, including the X-ray. I have been looking for many years for an undoubted case of giant-cell sarcoma of the bone of the epulis type which had killed with metastases in the lungs. I have been unable to find such a case.

In regard to the treatment of these cases, which is really what the pathologist has to decide, my position is that none of these tumors should be cut into. You may not get a diagnosis. That so often happens in my experience that I prefer to rest the diagnosis on the clinical history, the age of the patient, the X-ray findings, and the general physical condition of

the patient and the tumor. I agree with Dr. Martland that you cannot make a positive diagnosis in all these cases, but an incision does not always do it. I know many cases that have lost their limbs, and several that have lost their lives, from infection from bone cysts after exploratory incision and curettage. Many of them do badly, and Dr. Martland's patient is very fortunate indeed to have escaped infection in so many operations. Another reason for reaching this decision is that the benign tumors of this sort respond very well to treatment by physical agents, X-ray and radium. So also do the myelomas. In the malignant osteogenic sarcoma no method of treatment is satisfactory or successful, yet prolonged X-ray and radium treatment of osteogenic sarcomas in at least two cases has caused a complete disappearance of the local tumors, and the patients have remained well for three and a half and four and a half years, respectively, so that I would like to see what thorough X-ray treatment would do with the malignant osteogenic sarcomas. It is however difficult to get an opportunity to carry this out, for the patient will sooner or later fall into the hands of some surgeon who will cut the leg off. I have not been able to get a fair test of these tumors, but I am optimistic enough to say that if the limb could be immobilized and thorough X-ray or radium treatment be given over long periods the result might very likely be better in a series of cases than it is at present with amputation.

DR. MARTLAND: In reference to Dr. Moschcowitz's question, I do not believe that benign giant-cell sarcoma as I have described it ever does metastasize. I know there are a few cases on record in which it is claimed that the stroma has undergone so-called sarcomatous proliferation, but this has been very rare in giant-cell tumors, and I think those tumors which have metastasized have been the so-called periosteal or osteogenic sarcomas, in which you get a number of foreign-body giant cells, but you also get true tumor giant cells.

I agree with Dr. Ewing that some of the most eminent surgeons, who have had the best experience in bone sarcoma, seem to have no idea at all of what they are dealing with pathologically, and it is unfortunate that in the large cities we see extensive sacrifices of limbs which are absolutely unwarranted.

---

# PRIMARY SPINDLE CELL SARCOMA OF THE LIVER ASSOCIATED WITH CIRRHOSIS

MORTON RYDER, M.D.

*(From the Pathological Laboratories, Bellevue Hospital, Dr. Douglas Symmers, Director, New York)*

The reported cases of primary sarcoma of the liver have been collated by different authors, the latest collection being that of

Marx in 1904—57 cases. Marx analyzed many of these cases only to condemn them. He accepts the majority as sarcomatous, but thinks that the evidence of their origin in the liver is unsatisfactory. Some cases were attended by smaller tumors in other organs, such as the adrenal or the periosteum of the vertebræ that Marx considers may have represented primary growths. Others were incompletely investigated post mortem or lacked autopsies altogether, the diagnosis being based on operative findings. Marx concludes, however, that when all these cases are excluded there remain a considerable number of undoubted primary sarcomata of the liver. Others have still further reduced the number of unchallenged cases by questioning the sarcomatous nature of many of the growths. Ewing emphasizes the danger of classifying growths with an alveolar structure as of connective tissue origin, and points out the resemblance of some of the tumors reported as angiosarcomata to atypical carcinomata. The rarity of cases acceptable to all makes it a duty to report the following, in which the diagnosis of sarcoma appears to be unquestionable, and in which there is no reasonable doubt that the growth had its origin in the liver.

The patient was a laborer, aged forty-seven, born in this country. The family history was uncertain; he denied venereal disease and the use of alcohol and tobacco. He professed to have had no severe illnesses until fourteen months before his death, when he suffered from an acute abdominal attack with pain in the right upper quadrant. He did not know whether he was jaundiced at that time. A diagnosis of gall stones was made and at operation a fistula was made from the gall-bladder to the abdominal wall; this fistula remained open until death. He did not know whether gall stones were found. He returned to work and remained well until February, 1921, when his legs and scrotum commenced to swell. He was admitted to Bellevue Hospital on the service of Dr. Charles Nammack on February 16, 1921, and died eleven days later. During his stay in the hospital the patient was intensely jaundiced and moderately emaciated; mentally he was dull, not being aware of either the jaundice or the emaciation.

There were physical signs of pneumonia over both lower lobes. Examination of the heart was negative. In the epigastrium and right hypochondriac region there was felt a hard, nodular mass which corresponded in position to the liver and descended with inspiration. There was a ventral hernia at the site of a healed upper right rectus incision; at the upper end of the scar there was an open sinus discharging mucoid material. The scrotum

and both lower extremities were moderately edematous. During his stay in the hospital he had a temperature range of 98° to 100°, pulse 100 to 120, respiration 20 to 24. The leucocytic count was 10,200 with 84 per cent. polymorphonuclears; red cell count, 4,000,000. The urine was negative except for the presence of bile. A provisional diagnosis was made of carcinoma of the gall-bladder with extension to the liver. Pneumonia was apparently the immediate cause of death.

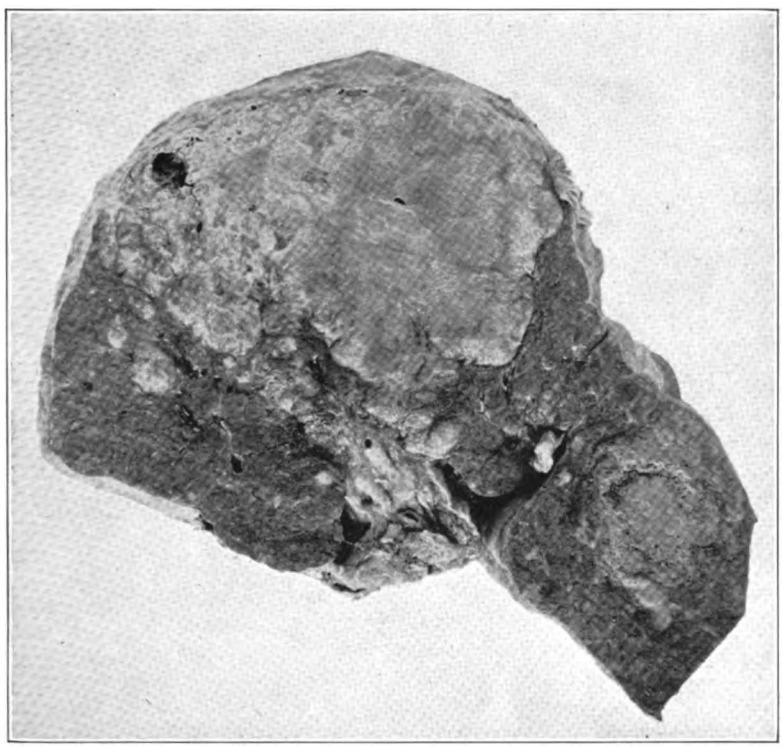


FIG. 1. Transverse section of liver through longest diameter.

*Autopsy:* The body was considerably emaciated, the abdomen slightly scaphoid. There was a moderate, soft, pitting edema of the lower extremities, scrotum and posterior body wall. The scleræ, skin and all the body tissues were intensely and uniformly icteric. There were large purpuric spots on the dorsum of both wrists and about the knees. The scar of the right rectus incision was recently healed at the upper extremity where the sinus had opened. The firm, nodular mass described could be felt two inches below in the xiphoid and just at the costal margin in the right mammary line.

The peritoneal cavity contained about 300 c.c. of thin, reddish-brown

fluid. The entire visceral and parietal peritoneum was studded with slightly elevated, rounded, grayish-white nodules, measuring 1 to 2 cm. in diameter. The omentum was adherent to the cæcum.

The liver was about normal in size but very firm and tough. The liver substance was broken up by trabeculæ of white fibrous tissue distinctly seen on section, between which bulged out little nodules of brownish liver tissue. The surface was nodular, apparently from the same cause, the nodules varying in size from one to several millimeters. In the right lobe was a spherical mass, about 10 cm. in diameter, consisting of firm yellowish tissue mottled with areas of a salmon color, and everywhere streaked with

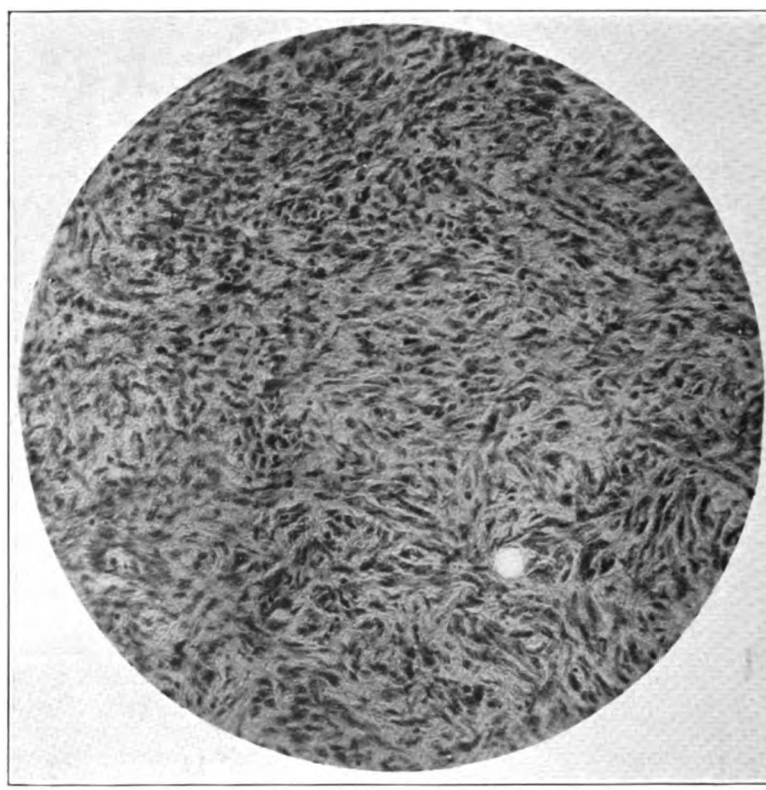


FIG. 2. High power photomicrograph of well-preserved portion of growth.

barely visible grayish fibers. There were some portions which were lighter yellow and very soft, but the major portion was as firm as the surrounding liver tissue. This mass was rather sharply circumscribed, but had no definite capsule. It projected slightly from the upper surface of the liver to form an irregular, white, firm protuberance over the major portion

of the right dome. Scattered throughout the liver were smaller nodules of similar tissue, some deeply imbedded, some on the surface. Those on the surface showed very slight umbilication and some showed central yellowish areas of softening. None of these masses was in close proximity to the gall-bladder, which was found in its normal site. The wall of the gall-bladder

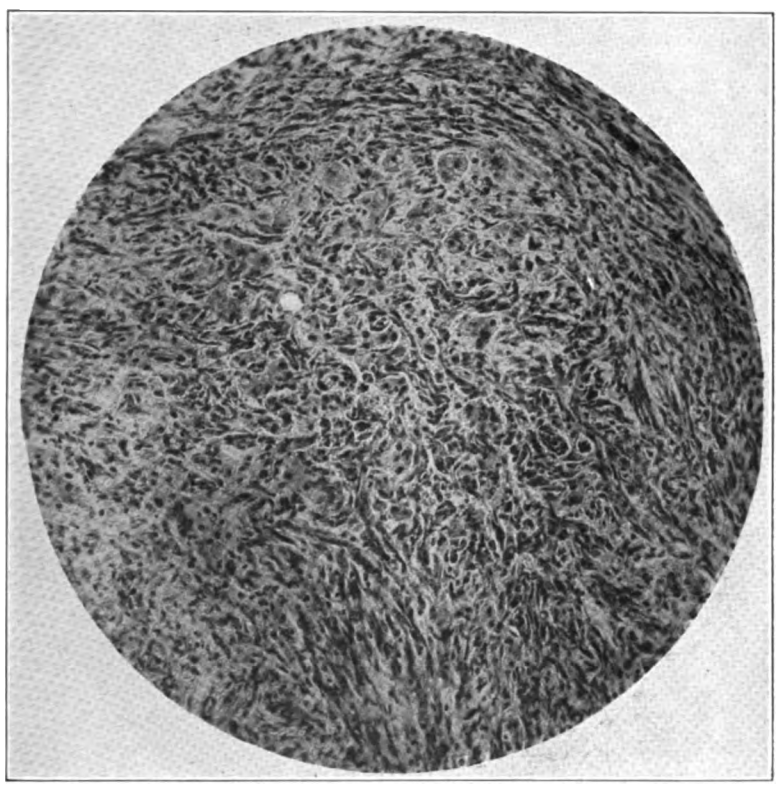


FIG. 3. Low power photomicrograph of margin of growth, showing islands of liver cells cut off completely by the tumor cells. These cells are loaded with yellow granular pigment.

was thin and flexible, its mucosa apparently normal. From the fundus of the gall-bladder a sinus extended to the upper end of the abdominal scar, surrounded by dense white scar tissue. The duodenum and transverse colon were firmly adherent to the gall-bladder. They were opened before being dissected free and found to be normal. The œsophagus, stomach and small and large intestines were carefully explored, but no ulceration or tumor was found. Above the pancreas, from the head to the middle of the body, was a mass of discrete nodules of tumor tissue, suggesting replacement of lymph nodes. The pancreas was entirely separate from this mass and appeared

to be normal. This chain of nodules extended to the portal structures, where they surrounded and pressed on the portal vein and common bile duct.

There was a similar mass of tumor tissue, measuring 1 x 3 x 4 cm., lying in the anterior mediastinum, just above the diaphragm. Both pleural cavities were partially obliterated by adhesions; the right contained about 300 c.c. of thin, amber-colored fluid. The visceral pleura over both upper

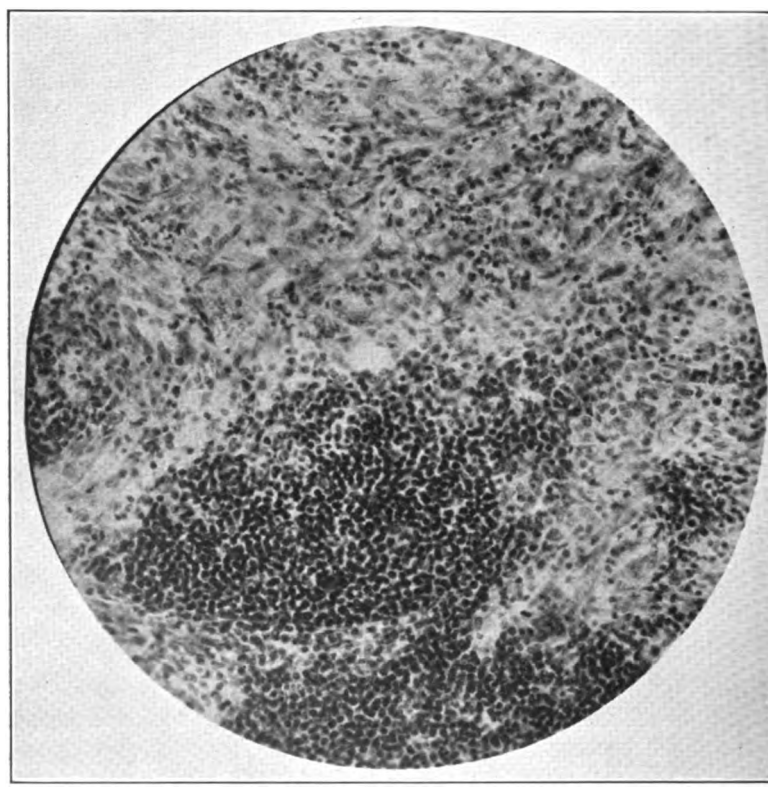


FIG. 4. Metastatic nodule in suprapancreatic lymph node.

lobes was studded with nodules similar to those in the peritoneum. There were healed tuberculous scars in the pleura at both apices. Both lungs were congested and edematous throughout, and there was patchy consolidation in the left upper and lower and right lower lobes. There were no nodules of tumor tissue in the lungs. There was complete obliteration of the pericardial cavity by fibrous tissue.

The spleen was twice the normal size, soft and flabby, and, on section, raspberry-red in color with no focal changes.

The kidneys, adrenals, ureters, bladder, prostate, seminal vesicles, testes, epididymes, larynx, pharynx and thyroid were free from metastases and were essentially normal. No palpable enlargements were made out in the bony skeleton. Examination of the brain and spinal cord was not permitted.

*Microscopic Examination:* Microscopically, the well-preserved portions of the growth showed a uniform structure of large spindle cells lying in fasciculi, so that they were cut in all directions. They varied somewhat in size, but, in general, were large; the nuclei were oval, rich in chromatin and had no definite nucleoli. Mitotic figures were numerous. Occasionally there was a cell with two or three closely crowded nuclei, but these did not form a prominent feature of the growth. Blood vessels were rather scanty and they had no apparent influence on the structure or nutrition of the growth. There was no alveolar arrangement in any part of the tumor. Intercellular stroma was practically non-existent in some areas. In other places there was abundant hyaline transformation with a few scattered, elongated spindle cells. Other areas were frankly necrotic.

The liver tissue showed a high grade of cirrhosis, chiefly perilobular in type. There were wide bands of fibrous connective tissue with rich lymphocytic infiltration surrounding individual lobules or groups of lobules. In some places the connective tissue had grown between the cell cords. The liver cells toward the periphery of the lobules were loaded with pigment in yellowish-brown granules and the intercellular bile capillaries were distended with bile.

The tumor encroached directly on the liver tissue, without the intervention of a capsule, and tumor cells were seen growing into the liver lobules, enclosing finally small groups of liver cells or even individual ones loaded with granular pigment. There were numerous lymphocytes scattered through the growth, particularly in close proximity to the portal spaces.

The suprapancreatic nodes showed a pure spindle-cell growth with no necrosis or areas of hyalinization.

Of the tumors found, that in the liver clearly should rank as primary, and those in the lymph nodes, anterior mediastinum, pleura and peritoneum as metastatic.

Pure spindle-cell sarcomata of the liver were found only twice in a review of the literature, but many tumors were classed as spindle- and giant-cell, or spindle- and round-cell. The association with cirrhosis is interesting. Rolleston and Trevor collected seven cases, including one of their own, only one of which was a pure spindle-cell growth. In this the author found it impossible to say whether or not the cirrhosis antedated the tumor. In our case the cirrhosis is uniform throughout the organ and is of an advanced grade. In many of the nodules tumor cells are seen

growing in the inflammatory tissue in the portal spaces, so that the possibility is suggested of a multiple origin of the growth secondary to the cirrhosis.

*Addenda:* Acting on a suggestion made during the discussion, preparations of the liver have been stained by the Levaditi method for spirochætes and by carbol-fuchsin for tubercle bacilli, but no organisms have been found.

The following brief notes of two cases resembling ours quite closely are appended:

1. From Arnold, In *Ziegler's Beitrage,* 1890, viii, 123. A man, fifty-three years old, for six months before his death had increasing jaundice, ascites and edema of the feet. He was in the hospital for one month. A hard nodular mass was felt in the epigastrium. Paracentesis was done twice, removing blood-tinged fluid. At autopsy, he presented intense jaundice and moderate ascites (the abdomen contained six liters of bloody fluid). There were pea-sized nodules throughout the omentum and mesentery, a few in the serosa of the intestine and a few in the pleura and bronchial nodes. The liver was much enlarged, coarsely granular and icteric. There was much interlobular connective tissue, sometimes enclosing several lobules, more marked near the tumor. In the right lobe was a tumor measuring 13 x 10 cm. and reaching the capsule; there were several smaller tumors in the vicinity and a beet-sized nodule at the base of the pericardium. Microscopically, the growth showed round, angular and spindle-shaped cells and a few giant cells. They grew around the blood vessels and seemed to spring from the adventitia. Arnold felt that the histogenesis was not certain, but that the sarcomatous nature of the tumor was undoubted.

2. From W. W. Ford, *Amer. Jour. Med. Sc.,* 1900, p. 413. A man, aged 59, with a markedly alcoholic history, died as a result of cerebral thrombosis. His abdomen had been increasing in size for some time. At autopsy, he presented no jaundice. The abdomen contained 4,000 c.c. of clear yellow ascitic fluid. The mesentery and omentum were filled with small nodules the size of a pea, white or reddish; similar nodules were scattered over the peritoneal surface of the abdominal muscles and diaphragm. The liver was small and showed an advanced grade of cirrhosis, principally intralobular. There was a tumor measuring 5 x 8 cm. in the right lobe. The center was soft, white and friable, the peripheral portions firm and grayish white. Microscopically, it consisted of round and spindle cells with central necrosis. The metastases were of the same structure with many blood vessels.

*Discussion:*

DR. EWING: I should like to express my great interest in this case. I have never seen anything like it. I do not feel that there is any definite

ground on which one can successfully attack the diagnosis. It is unique in my experience, and as far as I know, there is nothing exactly like it in the literature.

DR. NORRIS: I have not had a very good look at the section. It was under low power, and I would not want to say anything about it. The question of these sarcomas of the liver is however occasionally very difficult to decide. I remember I reported the case of a woman before this Society six or seven years ago, in which Dr. Hermann M. Biggs made the clinical diagnosis of primary sarcoma of the liver. It was a very large liver, weighing two or three pounds, and at autopsy there was found an epithelioma just above the cardia of the esophagus. The sections of that tumor are strikingly like a sarcoma and I presented it, and received considerable credit and discredit for bringing it to the Society just for diagnosis. I suppose in that case, where there was a distinct primary tumor at the lower end of the esophagus, the only fair conclusion was to call it a carcinoma, but that tumor as I recollect was very vascular and had a tendency toward alveolar formation and distinct large spindle cells. This tumor to-night evidently has small spindle cells, and apparently has no resemblance to a carcinoma or an epithelioma. It seems to me with the hasty examination I have been able to give it that the diagnosis of primary sarcoma is the correct one.

DR. EWING: Did you consider the possibility that this might be a peculiar granuloma? There are a great many lymphocytes all through the tissue. The general behavior of this tumor seems to me not that of a sarcoma. The tumor is not very bulky. It seems to replace the liver rather than to cause a great increase in the bulk of the tissue. It invades the lymph nodes, which sarcomata do not do, as a rule, and it is not in the lungs. There is very extensive necrosis in the tumor, which suggests doubt as to its nature. I am not convinced that this is properly to be classed as a simple sarcoma. What is sarcoma anyway?

DR. NORRIS: May I have another word? Although I hesitate to mention it, in all these rare tumors of the liver one must always think of melanoma, though it seems extraordinary to bring it up in reference to this case. Melanomas are so variable that a primary tumor might have been neglected or overlooked. I see no reason for thinking it is a melanoma, but I remember one case of a woman who had an eyeball tumor about six years ago. She had a melanoma, and an ovarian tumor with melanoma in it, with adrenal metastases.

DR. RYDER: The presence of the lymphocytes was not overlooked. They were found in greatest numbers in the inflammatory tissue in the portal spaces, and we considered them part of the inflammatory process in the liver rather than an integral part of the tumor.

# A REPLY TO DR. JOHANNES FIBIGER ON THE SUBJECT OF IRRITATION TUMORS

FRANCIS CARTER WOOD, M.D.

*(From Columbia University, Institute of Cancer Research)*

On December 8, 1920, at the request of Drs. Bullock and Curtis, I presented before this society a report of some experiments done in the Institute of Cancer Research on the artificial production of sarcoma of the liver in rats. That Dr. Fibiger received from the published account of these experiments the impression that Drs. Bullock and Curtis did not appreciate the importance of his work on *Spiroptera* cancer is evidenced by a letter received from him. Since he is displeased with their account it seems advisable to give to the society in his own words the corrections he thinks should be made in their statements:

DR. FRANCIS CARTER WOOD

*Dear Sir:* I have received the valuable paper of Bullock and Curtis: "The Experimental Production of Sarcoma of the Liver of Rats,"[1] and I beg you to accept my most hearty thanks for forwarding it to me.

I cannot, however, conceal that I have been highly surprised on seeing the incorrectness with which Bullock and Curtis have reported various particulars of some of my previous papers, and I shall therefore beg to address to you the following remarks, reserving, as a matter of course, my entering occasionally a public protest against the way of reporting used by Bullock and Curtis.

In the paper in question (p. 150) they write that "he (Fibiger) obtained 54 tumors (*Spiroptera carcinomata*) in the 134 animals which lived for 30 days or longer." In my paper: "Investigations on the *Spiroptera* Cancer III" (*Det. Kgl. Danske Videnskabernes Selskabs Biologiske Meddelelser*, 1918), p. 17, I distinctly wrote that "out of the 134 rats which lived in the space of time concerned, 18 were subjected to no sufficient microscopical examination or to none at all." Thus, it was impossible to include these 18 rats in the table showing the frequency of the *Spiroptera* carcinoma (p. 18). The 54 tumors, then, were not found among 134 rats, as reported by B. and C., but among 116 rats, and it cannot be known whether or not carcinomata would have developed in the remaining 18 rats.

When the authors write further: "In 8 of the 84 cases he (Fibiger) observed lung metastases," this statement, too, is wrong. Pages 25–26 in

the paper quoted, the following passage will be found: "Altogether, in special examinations on metastasis formation, metastases have, thus, till now been found in 8 out of 33 rats, and in 2 of 3 white mice, mentioned above, in whose stomach *Spiroptera* cancer had developed." This permits of no misconception and it is beyond excuse when Bullock and Curtis are giving the number of the rats in which metastasizing carcinomata were found as being 8 out of 84, as my paper contains the statement: 8 out of 33, no special examination on metastasis formation having been performed in the remaining 51 cases.

But the errors of Bullock and Curtis still seem to culminate in the following passage (p. 152 of their paper). They write here: "Fibiger and Bang reported the development of 22 carcinomata and 2 carcinosarcomata in 26 (tar-painted) mice which lived six months or longer. Of these tumors, 6 metastasized in the axillary lymphnodes and 2 in the lungs, and 3 grew on transplantation. Thus so far a great amount of labor and a large number of animals have been required to produce a few tumors, most of which are not transplantable."

How the fact that malignant growths were produced in 24 out of 26 tar-painted mice can be characterized by Bullock and Curtis as a production of "a few tumors," must be completely inconceivable to any rational reader. But still worse is the next passage: "most of which are not transplantable." Page 23 of Fibiger's and Bang's paper quoted by the authors contains the following passage: "Attempts were made in 3 cases to transplant the developed carcinomata, but in 2 cases without success. In one case transplantation gave positive result." On pages 26–27 successful transplantation of a carcinosarcoma is reported, and on page 32, that transplantation experiment was effected with positive result in one case of tar carcinoma.

Transplantation experiments, thus, were made altogether in 5 cases, and in 3 of these with positive result, and it remains unknown whether or not the remaining 19 tumors (out of the 24) would have shown transplantability, transplantatation experiment being not performed in these cases.

To any reader this will be quite clear. Bullock and Curtis, thus, impossibly can have any idea as to the frequency of transplantable tar growths, and their report concerning the transplantability of these tumors is perfectly wrong and misleading.

A correct description of the transplantation experiments made by Fibiger and Bang rightly ought to have run as follows: "Fibiger and Bang have made transplantation experiments only with 5 tumors, out of which no less than 3 were transplantable." That this number must be considered very great is an obvious fact, because transplantation of keratinizing tumors, as commonly known, will frequently meet with great difficulties (see Fibiger, Investigations on the *Spiroptera* Cancer VI, page 16, *Det. Kgl. Danske Videnskabernes Selskabs Biologiske Meddelelser,* 1919). Nevertheless, transplantation turned out successful with 2 out of 4 keratinizing transplanted tar carcinomata.

And Bullock and Curtis, no doubt, then would have omitted the point 8 of their summary, in which they speak of the "sharp" contrast of the transplantability of the cysticercus sarcomata with the "few" transplantable growths reported by other investigators.

I may add that the authors do not even mention the successful transplantation experiment made by Yamagiwa in a case of tar sarcoma of the breast of a rabbit, quoted in the paper of Fibiger and Bang. I beg you to be sure that these remarks are impelled not only by my personal wish to have a correct report of my investigations, but besides, by a regard for you yourself and for your Institute. Previously (in the *Journal of Cancer Research*) I have pointed out some incorrectness of Bullock and Rohdenburg's report of my former investigations, and I should now prefer to avoid a repeated criticism, which certainly would not increase the respect rightly due to Bullock and Curtis'—in other respects—very valuable paper.

Seeing in the report of the discussion, held in the New York Pathological Society, the remarks of Dr. Rohdenburg on my slides (p. 173), "If you take some of his (Fibiger's) and put them beside ours without seeing the labels, I doubt whether you could tell which was which," I should be very grateful if you would kindly send me such slides, belonging to the experiments of Bullock and Rohdenburg, as are demonstrating the correctness of these words. Certainly, Dr. Rohdenburg has examined some microscopical preparations of mine, and I don't believe Dr. Rohdenburg should have made the mistake of saying or supposing that the changes found in my slides were all in every place meant to be carcinomatous. Several of these preparations only contain carcinomatous changes in a few distinct limited places of the slides. But according to the plates published in the *Journal of Cancer Research* changes of this kind have never been found in the experiments of Bullock and Rohdenburg.

Yours truly,
(signed) JOHANNES FIBIGER

Dr. Fibiger's erroneous impression is no doubt based somewhat upon a previous publication by Bullock and Rohdenburg,[2] which questioned, and quite justly, the proof of the malignancy of irritation hyperplasias when based on morphology alone. Since this paper was published, however, further experiments with *Spiroptera* and with tar have added convincing biological evidence that malignant tumors have been produced by these agents; yet despite this Murray and Woglom[3] in a recent paper still repeat the caution that morphology is not a sure criterion of malignancy. Bullock and Curtis gave full credit to the several investigators who had produced malignant tumors by means of irritants, and it is to be regretted that there was any misunderstanding of their appreciation of the very great significance of these results.

The experimental production of cancer by irritants unquestionably opens a new field in cancer research, comparable to the

discovery of the transplantability of cancer, and it is unquestioned that Drs. Fibiger, Yamagiwa, and Ichikawa are the pioneers in the experimental production in animals of malignant irritation tumors.

But there are certain points raised in Dr. Fibiger's letter which are, in our opinion, the result of complete misunderstanding of the facts brought forward in our publication and require detailed discussion.

In reply to his criticism of Drs. Bullock and Curtis' treatment of his data dealing with the proportions of tumors and metastases, it should be explained that they treated his material exactly as they did their own. That is, the infested animals which survived to the cancer age were counted as negative unless there was known evidence that they were positive, even though they received only a macroscopic examination. In respect to their own data at least, it is certain that this is the fairer procedure. With the large amount of material handled in these experiments it would be humanly impossible to make a complete histological study of all the liver cysts in each animal autopsied. Therefore, reliance was placed chiefly on gross diagnosis confirmed in each case by microscopical examination. The parasite was removed from each cyst, and any cyst showing suspicious localized or diffuse thickening was preserved for microscopic study. A large proportion of the cysts which appeared negative macroscopically were discarded. A relatively small number, however, were retained and examined histologically in search of early sarcomatous changes. In this group a very few early sarcomata were found, but the proportion was small. Since malignant changes exist, before they can be recognized in the gross, as thickenings of the cyst wall, a few tumors were undoubtedly lost by discarding the animals in which no tumor or suspicious cyst could be recognized by the eye. However, since all the tumor-bearing animals and those with suspicious cysts were in the class examined, while the animals from which cysts were not examined appeared negative in the gross, it would be manifestly unfair to base the proportion of tumors only on the

former highly selected group. We naturally suppose that other investigators examine microscopically every suspicious lesion and discard only such animals as they believe to be negative.

Even the complete microscopic examination of every cyst from every animal autopsied would be an imperfect test of susceptibility, for in the observed cases the duration of the period of irritation associated with early sarcomatous transformation varied by seven months. The number of animals dead from other causes during this period, *i.e.*, from seven to fifteen months after infestation, which were negative at autopsy, but which would have developed tumors had they lived longer, is probably large in proportion to the number in which there was a malignant change in a cyst wall visible only under the microscope. That is, were it possible to make the complete microscopic examination of every cyst the error of counting certain susceptible animals as immune would be reduced but not eliminated. This type of error is inherent not only in all studies of susceptibility to irritation tumors but in nearly all studies of susceptibility to any particular disease. It is rarely possible to be positive that every negative individual is immune.

The culminating error by which Drs. Bullock and Curtis seem to have particularly offended Dr. Fibiger is the following statement: "Thus, so far a great amount of labor and a large number of animals have been required to produce a few tumors, most of which are not transplantable." This sentence, which is a separate paragraph, refers, as "any rational reader" will note, to all the investigations on irritation tumors cited and has no particular reference to Dr. Fibiger's experiments. At the time the statement was made we knew of only seven such tumors which showed growth on transplantation. This number includes the temporary growth obtained by Clunet,[4] and also the "tar sarcoma" (myxofibrosarcoma mammæ) of the rabbit produced by Professor Yamagiwa and his associates, to which latter tumor Dr. Fibiger refers in his letter. For the information regarding this transplantable tumor we were indebted to Fibiger and Bang[5] (page 8) who must have obtained their information from a

letter to Dr. Fibiger from Professor Yamagiwa. There is no description of a myxofibrosarcoma mammæ in the paper[6] referred to by Fibiger and Bang. This tumor no doubt is the one described by Yamagiwa, Suzuki, and Murayama,[7] in a publication received since the paper of Drs. Bullock and Curtis went to press.

According to these authors the transplantation experiments resulted in a few small growths, none of them larger than a grain of rice, but some of these which were examined microscopically showed evidence of growth. Propagation beyond the first generation was apparently not undertaken.

We do not wish to overvalue the material developed by Drs. Bullock and Curtis in comparison with that employed by other investigators, but it should be stated that the liver sarcomata which arose in the walls of the *Cysticercus* cysts were not subject to the difficulties of transplantation which Fibiger admits in the transplantation of keratinizing tumors.

Of the 43 *Cysticercus* sarcomata tested by homoplastic transplantation, only 2 failed to grow progressively. Some of the grafts from 1 of these 2 tumors showed temporary growth, the largest reaching the size of a white bean. The rat bearing this primary tumor showed small metastic nodules in the omentum. In the second case which failed to grow progressively on transplantation the tumor was infected and abscesses were formed at the sites of inoculation. That is, homoplastic transplantation of *Cysticercus* sarcoma is successful in a high percentage of cases.

A simple method of determining the malignancy of irritation tumors has been demonstrated by experiments described in a valuable paper recently published by Murray and Woglom.[3] These authors relied chiefly on the progressive growth of autografts (artificial metastasis) as the criterion of malignancy. The vast majority of *Cysticercus* sarcomata perform their own autoplastic transplantation, as is evidenced by the very general occurrence of peritoneal metastases, and, hence, do not require homoplastic transplantation to establish their malignancy.

We have examined the microscopical preparations of *Spiroptera* cancer to which Dr. Fibiger refers in his letter. While in some areas these experimental tumors suggest a type of epithelioma which occurs in man, we would not feel justified in calling such lesions epithelioma merely because they show morphological resemblance to epidermoid cancers. They do not exhibit the unrestrained invasive growth that in itself is diagnostic of malignancy; rather, they are localized epithelial reactions which show in one or more small limited foci a suggestion of infiltrative growth associated often with some degeneration or keratinization of the epithelium. In our opinion at least, one of the lesions which Dr. Rohdenburg mentioned in the discussion referred to by Dr. Fibiger simulates epithelioma as closely as any of the nine preparations of Dr. Fibiger's which we have studied. This lesion was described and figured (Plate 14) in the paper by Drs. Bullock and Rohdenburg.[2] They believed that the morphological evidence obtained in their experiments and in the early experiments of Fibiger[8] and of Yamagiwa and Ichikawa[9] was insufficient for a diagnosis of malignancy when unsubstantiated by biological proof. As stated in the communication which Dr. Fibiger criticizes, and restated in the present paper, the malignant nature of some but not all the growths produced in response to irritation by *Spiroptera* and by tar has been demonstrated conclusively by metastasis formation and by transplantability. We agree with the statement of Murray and Woglom that "it would be hazardous and inadvisable to attempt to decide whether the new formations described by our predecessors are in every case rightly included in the malignant new growths or not. It is even probable that some of the tumors regarded as benign by them would, if tested by autoplastic transplantation, have given evidence of progressive independent growth."

It is impossible to judge how important a rôle the interpretation of the lesions plays in the varying proportion of tar cancers reported by different investigators. In comparing their own results with Tsutsui's,[10] Fibiger and Bang[5] suggest that their relatively larger number of tar cancers may have been due to a dif-

ference in the tar used or to a difference in the susceptibility of the Danish and Japanese mice. Each of these factors may be partly responsible. Bloch and Dreifuss[11] have recently reported the isolation from coal tar of the agent effective in the production of tar cancer. It is possible that the proportion of this ingredient varies in coal tar from different sources. That there is in rats a difference in the susceptibility to *Cysticercus* sarcoma of strains and even of families within the same strain is already indicated by the experiments which Drs. Bullock and Curtis are carrying on, in which 440 of these tumors have so far been produced. A difference in susceptibility seems to be the most probable explanation of Schmitt-Jensen's[12] failure to produce *Cysticercus* sarcomata of the rat liver by experiments which in all essential particulars duplicated those of Bullock and Curtis.

In conclusion it seems to us that the several experimental methods of producing malignant tumors are supplementary and that coöperation between the investigators would prove advantageous in the solution of the problems which have already presented themselves in connection with these irritation tumors.

*References*


1. Bullock and Curtis: *Proc. New York Path. Soc.*, 1920, N. S., xx, 149.
2. Bullock and Rohdenburg: *J. Cancer Res.*, 1918, iii, 227.
3. Murray and Woglom: *Seventh Sci. Report, Imperial Cancer Research Fund, London*, 1921, p. 29.
4. Clunet: *Researches expérimentales sur les tumeurs malignes, Paris*, 1910, p. 297.
5. Fibiger and Bang: *Det. Kgl. Danske Videnskabernes Selskabs Biologiske Meddelelser*, 1912, iii, 4.
6. Yamagiwa and Ichikawa: *Mitt. a. d. med. Fakult. d. k. Univ. Tokyo*, 1919, xxii, 1.
7. Yamagiwa, Suzuki and Murayamo: *Mitt. a. d. med. Fakult. d. k. Univ. Tokyo*, 1920, xxv, 189.
8. Fibiger: *Ztschr. f. Krebsforsch.*, 1914, xiv, 295.
9. Yamagiwa and Ichikawa: *Mitt. a. d. med. Fakult. d. k. Univ. Tokyo*, 1915–16, xv, 295–344; 1917, xvii, 19; *J. Cancer Res.*, 1918, iii, 1.
10. Tsutsui: *Gann*, 1918, xii, 17.
11. Bloch and Dreifuss: *Schweizer. med. Wchnschr.*, 1921, li, 1033.
12. Schmitt-Jensen: *Den Kgl. Veterinaer-og. Landbohjskole aarsskrift.*, 1921, p. 91.

# Proceedings

of the

# New York Pathological Society

New Series. Vol. XXI. OCTOBER-DECEMBER, 1921 Nos. 6-8


CONTENTS

# ACTIVE IMMUNITY AGAINST EXPERIMENTAL PNEUMOCOCCUS TYPE I PNEUMONIA IN MONKEYS FOLLOWING INTRATRACHEAL INJECTION OF VACCINE

RUSSELL L. CECIL, M.D., AND GUSTAV I. STEFFEN

In a recently published article, we have shown that three large doses of pneumococcus Type I vaccine injected subcutaneously at intervals of one week produce a complete immunity in monkeys against experimental pneumococcus Type I pneumonia. Furthermore, we showed that satisfactory immunity can be produced by several *small* doses of pneumococcus Type I vaccine if the injections were made intravenously.

We have recently studied the effect of pneumococcus Type I vaccine when injected directly into the trachea of monkeys. As in the previous experiments, three inoculations were made, separated from one another by intervals of one week. The skin over the neck of the monkeys was sterilized with tincture of iodine and the vaccine injected through the skin into the trachea by means of a hypodermic syringe. The doses used were 20, 40, and 60 billion, making a total of 120 billion of killed pneumococci. The volume of vaccine injected was, in every instance, one cubic centimeter. In these experiments, as in previous experiments with pneumococcus vaccine, the immunity of the monkeys was tested two or three weeks after the completion of vaccination. As in previous experiments, all monkeys were killed at the end of the period of observation, in order to determine the presence or absence of pneumonia.

The results of vaccination by the intratracheal route were entirely satisfactory. The three vaccinated monkeys remained perfectly well, while the control developed a mild but very definite pneumonia from which he recovered.

We are now attempting to vaccinate monkeys by spraying their throats with pneumococcus vaccine. This experiment however has not yet been completed.

The intratracheal administration of pneumococcus vaccine appears rational in view of the fact that pneumococcus infection usually takes place by this route. We have shown in previous articles that immunity against pneumococcus may exist in the lung when no protective substance can be demonstrated in the monkey's serum. In the experiments with intratracheal vaccine this same phenomenon was observed, namely—complete immunity against pneumococcus in the lung and the entire absence of protective substance in the serum of the vaccinated monkeys. The protection tests were carried out on mice in the usual way.

*Discussion:*

DR. HUNTOON: I think this work of Dr. Cecil's and Mr. Steffen's is an extremely important contribution, in that it points the way to the ultimate path of medicine, which will be to prevent instead of to cure. Many interesting points have arisen here, particularly the one as to whether this is the production of the so-called local immunity. Is it possible to produce a local immunity of some particular organ which is not enjoyed by the rest of the body? Bordet's work on dysentery brought up this old question again. In his work the mucous membrane of the gut produces an immunity against dysentery, but I remember that Dr. Zingher told us before this Society that he had failed to induce any such immunity. I shall be interested to see how the spraying experiments come out, because this would offer a method of easy application of vaccines, and it would avoid the use of the needle.

MR. STEFFEN: In the spraying experiment we are spraying the monkeys with an ordinary DeVilbiss spray, and we intend to continue the spraying about three weeks. This is a very easy method of vaccination, and it does not produce any reaction. The monkeys remain perfectly lively. Even when we injected twenty, forty and sixty billion killed pneumococci into the trachea they did not show any local or general reaction.

---

## PRELIMINARY REPORT ON THE NATURE OF THE IMMUNIZING ANTIGEN OF PNEUMOCOCCUS, TYPE I

WILLIAM A. PERLZWEIG, PH.D.

The active immunity conferred upon white mice by the subcutaneous injection of heat-killed pneumococci (type I) and of various chemical fractions of the organism was studied. It was found that:

1. By using an initial small dose of vaccine followed by a larger dose a greater degree of immunity was produced in mice than by a single large dose or by repeated large doses of vaccine.

2. The nucleoprotein obtained from pneumococcus by treatment with anhydrous sodium sulfate (Rowland's method) or by alcohol precipitation from solutions of pneumococcus in bile salts carried the active antigenic fraction.

3. On autolyzing or digesting with proteolytic enzymes the entire organism or the protein fraction, the antigen was found in the digest unimpaired, being resistant to prolonged autolytic and tryptic action.

4. On the addition of the above digests to alcohol to make a concentration of seventy to eighty-five per cent. alcohol, the antigen was recovered in the alcoholic filtrate, but not in the precipitate. The antigen is not soluble in ninety-five to ninety-nine per cent. alcohol. The alcohol-soluble antigen is soluble in neutral, acid and alkaline aqueous solutions, but is not soluble in lipin solvents.

5. The antigen is not destroyed by boiling for five minutes if in neutral or slightly acid solution, but is impaired by boiling in alkaline solution.

6. The above methods of extraction of the antigen and the dependence of heat stability upon the reaction (hydrogen ion concentration) suggest the possibility of the antigen being closely related to the antineuritic vitamine, water-soluble B.

Further work on this subject is in progress.

*Discussion:*

DR. HUNTOON: This work of Dr. Perlzweig is revolutionary. I have known about it for some time because I have been doing somewhat similar experiments from a somewhat different angle. I can confirm a good many things that he has spoken of, and it has long been a belief of mine that we use too much antigen for the immunizing portion of the antigen is a very small part, and this can be proven mathematically. What he said about starting off with small doses is true. I have had a very wide experience with immunization of horses and I find that by giving a horse 0.1 c.c., which is a small dose in a 1,200-pound horse, then three days later 1 c.c., and then 5 c.c., you can get a horse up in three weeks as high as you can go. With

streptococci you can bring a horse up in ten days to that limit. If you start a horse with 5 c.c., you throw him out of condition, and get less antibody response. After you have once sensitized him you can go on. It seems to me that the aim of the bacteriologist who is interested in active immunity and protective inoculation should be to produce a non-toxic antigen which would give neither local nor general reaction, but which would give a rapid immunity. The difference in the rapidity of immunity produced by the injection of the whole organism and the injection of the extract is very considerable. In the one case it can be done in seven days. It is almost impossible to get a protection up to the same point by giving the doses of whole antigen extending over a period of three weeks. Why should the immunity in one case be much more rapid than in the other? You have taken the burden off the animal of disintegrating the antigen by putting it into a soluble solution so that it can be taken up by the cell that produces antibody. It is all a question of ferment action.

DR. PERLZWEIG: There are many intricate biological aspects of this problem that are quite difficult to solve, and which will require a good deal of time and labor. There is the question of the duration of the immunity after each of these antigens, which is a rather trying one. In some cases it seems to last quite well with the mice in question, and in some cases it does not last. Using a large number of animals, some succumb to a small dose of the infecting organism, while others, protected in the same way, withstand a very large dose of the infecting organism. I have had mice for two months after vaccination, some of which show a very good immunity at the end of that period, and others do not. There seem to be a great many factors to study that will require the exhaustive work of many men.

---

# THE SKIN REACTION IN BRONCHIAL ASTHMA AND ALLIED CONDITIONS

NILS P. LARSEN, M.D., ROYCE PADDOCK, M.D., AND HARRY L. ALEXANDER, M.D.

*(From the Second Medical Division, Bellevue Hospital and Department of Medicine, Cornell University Medical College)*

At the asthma clinic in the Out-Patient Department of Bellevue Hospital, observations were made on the "skin reaction" as a diagnostic aid in asthma and allied conditions. The mechanism of the reaction has not been established. That the skin reaction sometimes demonstrates the exciting cause of symptoms is a well-known fact. Since often no amount of questioning reveals the

cause and as the removal of it gives immediate relief, there is justification for continued study of the skin reaction as a diagnostic aid.

It is also well known that a certain proportion of individuals suffering with asthma or hay fever reacts by means of an urticarial wheal, when a small amount of the substance which can originate an attack is brought in contact with a scratch or injected into the skin. The wheal exhibits irregular edges, pseudopodia developing within twenty minutes, and is usually surrounded by an area of erythema, accompanied sometimes by swelling and other signs of inflammation. The site itches and occasionally remains red and swollen for several days. Regardless of method employed, a marked reaction in a definitely sensitive skin never is difficult to elicit.

*Comparison of Cutaneous and Intracutaneous Methods.*—More tests can be made with less trouble and time, at the same sitting with the cutaneous or scratch method. With dry preparations (used in the scratch method), however, there is no way in which to tell when they have lost their potency. With solutions (for intracutaneous injections), contaminations which destroy the potency can be readily seen. Also, when a precipitate forms in a solution, the potency may be decreasing. One such solution which had given very good reactions for several months developed a precipitate. Cultures proved it to be sterile. Upon testing, negative reactions were obtained in several skins which then reacted well to a fresh solution of the same protein.

Clinical results showed that the technical advantages of application in the scratch method were outweighed by the increased reliability of the intracutaneous method. To illustrate with a case: A. B. developed asthma only when in contact with horses. A horse could pass, or he could ride a horse for a few minutes without symptoms, but after close contact for four or five minutes, he invariably began to wheeze. On May 1, 1921, he was tested intracutaneously on the right forearm with a solution of horse dander prepared by Dr. Coca's method. Two inches away, on the same arm, a dry commercial preparation was applied by means of

a one-eighth-inch superficial scratch, upon which a drop of decinormal NaOH was applied, and then dry powder stirred into it. A control injection with horse serum was made. After twenty minutes, the intracutaneous reaction showed an irregular wheal 3 cm. by 2.5 cm., surrounded by erythema. The patient complained of itching at the site of injection. There was no reaction at the site of the scratch. The solution of horse dander, which gave this reaction, was controlled by injection into ten other asthma patients with negative results. The horse serum likewise gave no reaction. It was found that in fifteen similar instances, in thirty-one tests made, there was no definite response to the commercial preparation put on by the scratch method, although history of contact and intracutaneous methods were positive. The commercial dry preparations had been received within three months and then kept dry in the laboratory. The commercial pollen extracts gave a good reaction in most cases, whereas the dry products, especially the epidermal proteins, although effective in many instances, were so uncertain that they were unsatisfactory for routine use.

It is not possible to use the calibration devised by Walker in comparing these two methods. One can make no definite ruling as to the reading of reactions. The normal on an irritable skin cannot be compared with the normal on an unresponsive skin. It emphasizes the fact that the questionably positive reactions must be measured parallel with control injections on the same individual. These borderline reactions occur with the scratch as well as with the intracutaneous method. In such cases, an opinion can be arrived at only by repeated tests on different days, and with careful investigation of possible contact.

*Comparison of the Two Methods with the Same Solutions.*—To compare the scratch and the intracutaneous methods on the same individual with the same solutions, the following experiment was performed: Ten patients known to be sensitive to ragweed pollen were injected with three solutions of different strengths of this protein. These were freshly made solutions (Coca method) —Solution A, 1–100, Solution B, 1–1000, Solution C, 1–5000.

Weight of pollen in grams was the factor used in determining the strength of dilutions. The middle anterior one-third of the forearm was used, alternately placing the strongest solution superiorly and inferiorly on the different patients. Two inches away, and parallel with the injections, scratches were made about one-eighth of an inch long, and deep enough so that small red points were just visible. These scratches were kept covered with the various solutions for twenty minutes. The strongest solution was injected at the same time into two normal individuals, and had been used on many other patients routinely without reactions. Control solutions of other proteins had also been used on all these sensitive skins with negative results.

TABLE I

*Comparison of Strengths of Reactions to Cutaneous and Intracutaneous Applications of Ragweed Solutions of Varying Pollen Content, in Ten Sensitive Individuals*

| Solution | Positive | Doubtful | Negative |
|---|---|---|---|
| *Solution A* | | | |
| Intracutaneous | 10 | 0 | 0 |
| Scratch | 4 | 0 | 6 |
| *Solution B* | | | |
| Intracutaneous | 6 | 2 | 2 |
| Scratch | 1 | 1 | 8 |
| *Solution C* | | | |
| Intracutaneous | 5 | 2 | 3 |
| Scratch | 1 | 0 | 9 |
| *Solution A Control patients* | | | |
| Intracutaneous | 0 | 0 | 20+ |
| Scratch | 0 | 0 | 20+ |

Solution *A*—Ragweed Pollen Solution 1-100
Solution *B*—Ragweed Pollen Solution 1-1000
Solution *C*—Ragweed Pollen Solution 1-5000

It is, therefore, evident that certain individuals, whose asthma or hay fever is brought on by specific proteins, may give a skin reaction to a solution of that protein when it is injected intracutaneously and show no reaction when the same solution is applied by means of a scratch.

*Relation of the Size of Scratch to Size of Reaction.*—To determine whether the size of the scratch influences the size of the reaction, the following experiment was performed: As in the above experiment, the middle anterior third of the forearm was used. Eleven patients whose skins were definitely sensitive to ragweed were chosen. Two or more scratches of lengths varying from 2 mm. to 11.5 mm., and just deep enough to draw blood, were made. The scratches were covered with decinormal NaOH and dry ragweed pollen mixed with the fluid. The reactions were read in twenty minutes. The size of reaction in breadth varies with the length of the cut, but not proportionately. For instance, a scratch 11.5 mm. reacted by a wheal 11 m. in diameter, whereas, in the same patient, a scratch 2.5 mm. long gave a wheal 7.5 m. in diameter; 1 : 1 *vs.* 1 : 3.

Schloss[1] believes that the size of reaction varies, depending upon the location on the arm. To test this statement, fourteen sensitive patients were given intracutaneous injections of ragweed pollen solution at the elbow fold anteriorly and a second injection of this solution, of like amount, was given 10 cm. below. The reactions were read in twenty minutes. The reaction at the elbow was never smaller, and was usually larger than the reaction at the region nearer the wrist. There was always more erythema at the elbow site.

*Other Factors which Influence the Size of the Reaction.*—The strength of the solution brought in contact with the cells is another factor which determines the size of the reaction. This is shown in Table I where the same amount of fluid was injected in each instance. This fact has been made use of to determine the initial dose of prophylactic injections. When different quantities of protein solutions of equal strength are employed, a similar relation is noted. Eight sensitive patients were injected on the right forearm with 0.01 c.c., and 0.04 c.c. of a ragweed solution containing 0.3 mg. of nitrogen per c.c. The reactions were measured at the end of twenty minutes. The size of the wheal was shown to increase with increase in the amount of protein solution injected, though not always in direct proportion to it.

The skin reactions were, therefore, found to be influenced by the following factors:

(*a*) The preparation used.
(*b*) The method of application.
(*c*) The length of scratch made.
(*d*) The site of injection.
(*e*) The degree of cellular sensitivity.
(*f*) The amount of protein in contact with the cells, and the amount of solution injected.

*Local Skin Desensitization.*—A point still in question is local skin desensitization. Mackenzie[2] showed that by repeated injections at the same site on the same day, he could cause a disappearance of the reaction. This was repeated on two cases, as follows: The first was a male nurse sensitive to timothy pollen. He was injected nine times in the same site with timothy solution, 0.6 mg. nitrogen per c.c. The first injection was given at 9:30 A.M.; the last at 6:30 P.M. The injections were approximately one hour apart. After no injection did the skin fail to respond with a new wheal. After the eighth injection, the patient had symptoms of hay fever; also, two hours after the ninth. The eighth and ninth reactions were the largest, giving wheals with irregular edges and pseudopodia. The next morning, the forearm was still red and swollen, and another injection at the same site was followed by a markedly positive reaction.

The second case was a ragweed-sensitive patient. Four injections were given during the course of an afternoon. After no injection did the cells fail to respond, and there was apparently no decrease in reaction.

To test out the effect of weekly injections at the same site, two patients were used. After several injections, there seemed to be a definite decrease in the reactive power of these cells. The wheal became smaller, the erythema less, and when seen on the succeeding day, the site of repeated injection was clear. The control injection at a new site showed a larger reaction. One patient was sensitive to both ragweed and timothy. Both decreased as stated

above, and when after three months the injections were reversed, the cells responded as at a new site. Injections were then discontinued for a period of three weeks. When the site was then reinoculated, it responded as a fresh site. On the following day, it was still red and swollen as badly as the control site. The effect of desensitization was apparently only temporary, and there was no permanent increase or decrease in the power of these cells to react.

*References:*

1. Schloss, O. M.: *Am. Jour. Dis. Child.*, 1921, xix, 433.
2. Mackenzie, G. M.: *Proc. Soc. Exper. Biol. and Med.*, 1921, xviii, 214.

*Discussion:*

DR. ZINGHER: I am certain that we have all appreciated this interesting communication of Dr. Alexander. There are certain points that stand out in these intradermal tests in cases of hay fever and bronchial asthma that seem to me worth emphasizing. Anybody who has had the opportunity of seeing these tests carried out at the clinic conducted under the directions of Dr. Cooke and Dr. Coca at the New York Hospital will be impressed with certain facts.

The intradermal test seems to be highly specific. I recall just now an interesting instance of two children in one family, both of whom were suffering from asthma, and who applied for testing and treatment at different times at the clinic. In both children there was a marked reaction to an extract of rabbit's hair, and little or no reaction to the other tests. Inquiry showed that these children had slept on small pillows stuffed with rabbits' hair. Many cases of hay fever, also, give a strong reaction to a single pollen extract. This strong susceptibility is also evident in many asthmatics to individual epidermal extracts or cereal extracts.

Quite a number of these patients show a multiple sensitization to extracts from various groups; as for instance, the pollens, the epidermal extracts and the cereal groups. In some individuals one of these reactions seems to be most prominent, in others several reactions are equally prominent. I understand, however, that desensitization with an extract of the antigen that gives the most prominent reaction will also desensitize the patient against the other substances, to which he is sensitive.

The intradermal test seems highly sensitive. Many individuals give what are called negative reactions, although wheals varying in diameter from 0.5 to 0.75 cm. appear at the site of the test injections. Often it is difficult to decide whether the reaction is negative or moderately positive. Some individuals show equally prominent wheals at the site of all test injections. The diagnostic one when present appears distinctly enough as a very prominent wheal with peculiar pseudopodia prolongations. Owing to these doubtful reactions it seems quite important that fairly exact and equal amounts of the different test fluids should be injected.

DR. MACKENZIE: In the last few years there has been a great increase in the application of cutaneous reactions, and with the more widespread use, there has been a good deal of uncritical interpretation of the reaction. It is helpful and important to have such accurate observations as those which Dr. Alexander has reported to-night, and they are going to help clarify the problem. The procedure is simple, but the interpretation difficult. My experience with the cutaneous or scratch method and the intracutaneous method corroborates a good deal of what Dr. Alexander has said. There is no question about the greater delicacy of the intracutaneous test. Many patients will react to it, and not to the cutaneous test. I have in mind however, one experience which I think is worth remembering when doing reactions on patients who are highly sensitive. The patient was a sufferer from hay fever and bronchial asthma in the autumn. In doing a scratch test with a 1 : 100 dilution of ragweed there was only a questionable reaction. There was a little reddening, but not a definitely positive reaction. I then tried an intracutaneous test with a solution of ragweed containing 0.01 mg. of nitrogen per 100 c.c., made by extracting pure ragweed pollen with one one-hundredth normal sodium hydroxide. In a few minutes there was a large wheal four or five cm. in diameter. This went on for thirty minutes or so, and then began to subside. It was going down, and the patient had no further immediate symptoms. That night her arm swelled from the wrist to the shoulder; she had violent asthma, and broke out into urticaria over the entire body. She was confined to her bed for forty-eight hours.

As for the local exhaustion to which Dr. Alexander has referred, with Dr. Baldwin I have in press now a paper on that subject which reports observations made in the Presbyterian Hospital on a group of eight patients, repeating the test at the same site at short intervals. This was done by both intracutaneous and cutaneous methods. We found without exception that it is possible to exhaust the site locally, so that the reactivity is abolished. We found further that the exhaustion is much more rapidly effected with substances presumably more antigenic than ragweed extract. Horse serum and egg albumin have given the most striking exhaustion. However, even with our preparation of ragweed, which I presume is different from that used by Dr. Alexander, it has always been possible to exhaust the site locally, although it has taken a good many more applications than with such substances as horse serum or egg albumin. We have not tried the exhaustion method which Dr. Alexander reports, that is, repeating the tests at intervals of a week, but it is very interesting to know that at least a partial exhaustion may be accomplished in that way. I cannot feel that his failure to corroborate our observations on those two patients is of very great significance. The preparations are different, and it seems possible that exhaustion would have been accomplished if carried further. At any rate, our thirty-six consecutive attempts on eight hypersensitive patients exhausted the sites locally.

DR. THOMAS: Have you any theory to account for the variability in response to the tests for cutaneous sensitiveness, and have you noticed that patients during an attack of asthma are less sensitive to the proteins? Have

you any theory also to account for the fact that there is such a discrepancy in one patient's reaction to the same test from time to time?

DR. ALEXANDER: In regard to Dr. Mackenzie's remarks, we are apparently using ragweed solution made in a different way from his, so that may account for that discrepancy. I think he has more evidence than we have, as he has eight patients and we only have two.

As to the variability in these reactions, they are very delicate and variable in so far as constant results can be obtained. There are several different factors that influence the size of the reaction, as I pointed out, and after all when size crosses the threshold from a negative to a doubtful to a positive test one must be very careful in the interpretation of the results and comparisons can be made only by repeated drawings of the reactions. During an attack of asthma it is considered probable that these skin reactions do diminish. I confess it has been our experience that they are not completely wiped out, and an attack of asthma does not seriously affect the reaction. With the exhaustion from week to week we were able to reduce reactions very materially as compared to a control site on the same arm at the same time.

We also have had a few cases where the inflammation spread up the arm after intracutaneous tests. Walker describes similar experiences with the cutaneous method. In none of these has there been any permanent damage, although occasionally a temporary attack of hay fever and asthma has been induced.

---

# TWO CASES OF HUMAN ACTINOMYCOSIS

PAUL F. RUSSELL, M.D.

(*From the Department of Pathology, Bellevue Hospital, Dr. Douglas Symmers, Director*)

Actinomycosis in New York is not a common disease apparently, for there are records of only five clinical cases in Bellevue during the past fifteen years and among the last seven thousand autopsies in the Bellevue laboratories the two cases presented in this paper are the only ones on record. It is of course possible that one or two cases have not been diagnosed clinically but it is not at all probable that cases have been missed at the autopsy table, for sections from each case are studied microscopically.

The frequency of this disease in the United States may be judged from the fact that Erving[1] in 1902 was able to collect only one hundred cases, although the first case in this country had, according to Frazier,[2] been reported seventeen years previously, in 1885, by Murphy.

Actinomycosis is said to be more frequent in England and on the European continent. There were for example one hundred and thirty-five cases of actinomycosis in the London hospitals between the years 1902 and 1912.[3]

The first case to be presented is that of a male negro, aged forty-four, born and resident in the United States, a porter by occupation. He was admitted to a New York hospital September 2, 1920, complaining of pain in the right inguinal region of a week's duration. His family and past history were negative. Physical examination revealed some tenderness in the region of the pain and a marked psoas spasm on the right. The patient's temperature was 99° F. and the white blood cell count was 17,000 with 80 per cent. polynuclears. The condition was diagnosed as probably an appendiceal abscess that had ruptured retrocecally. An operation the following day demonstrated a deep abscess in the right lower quadrant from which several ounces of pus were evacuated. The character of this fluid is not recorded. The surgeon found it "impossible to determine the source of the pus" but the process had extended dorsally to the posterior peritoneal lining and anteriorly to the face of the ilium. A smear of the pus showed short chains of streptococci. No growth resulted from an attempted culture.

After a convalescence not apparently unusual the patient was discharged, twenty-three days after admission. The wound had gradually closed and was not draining. The final diagnosis was, "Abscess of right inguinal region."

One month after his discharge the patient was readmitted, complaining of fever, saying that he was sick. Examination of the operation wound showed slight oozing of pus and there was again a marked psoas spasm. His temperature was 99° F. but rose that night to 101.6° F., returning to about 99° F. the next morning. At operation the day after readmission the granulating wound was curetted and a large cavity remained extending down to the brim of the true pelvis and up nearly to the attachment of the psoas. No cause was found for the failure to heal.

Blood chemistry was negative, the non-protein nitrogen being 32 mg. per 100 c.c., creatinine 1 mg. per 100 c.c., sugar 90 mg. per 100 c.c., and the blood Wassermann test was negative. The urine on readmission had been negative but a month afterwards it contained albumin in fair amounts. The patient was exposed to Roentgen and to sun rays. He was given massive doses of potassium iodide, but there was no improvement in his condition. For eight months he remained in this first hospital with continual drainage from the wound and a gradual failure of his general constitution. A diagnosis of tuberculosis was made, the focus being thought to be probably in the right kidney.

On June 22, 1921, the patient was discharged to Bellevue. This was ten months after his admission.

At Bellevue the man was seen to be markedly emaciated. He had a large granulating wound in the right lower quadrant with marked bulging. His lymph nodes were not palpable. The local condition was described as fol-

lows: "Large areas of protuberant granulations the size of one's hand. Tissue very soft and vascular and does not resemble chronic inflammatory tissue. It is not fibrous. It is possibly a new growth. There is much bleeding from the granulations."

A bacteriological report at this time was "prevailing organism a Gram negative, slender, non-motile, encapsulated bacillus growing readily in ordinary media but not characteristic of any known pathogenic organism."

Biopsy demonstrated "infected granulation tissue. There are some deep staining bodies suggesting actinomyces."

Repeated smears, however, did not reveal actinomyces.

A blood count showed white blood cells 7,000, red blood cells 1,600,000, hemoglobin 35 per cent. The urine contained albumin and pus.

Five weeks after admission to Bellevue the patient went into a delirious state and died. This was July 30, 1921, a year, lacking a month, following the onset of his symptoms.

The body was autopsied by Dr. Morton Ryder and myself and the following anatomical diagnosis was recorded:

Retroperitoneal actinomycosis invading the right ilium, the lumbar vertebræ (2, 3, 4, 5), the right kidney and the retroperitoneal lymph nodes. Localized pelvic peritonitis. Superficial ulceration of the bladder. Mural thrombosis of the inferior vena cava. Multiple infarcts of the lungs with gangrene. Renal calculus in left kidney. Hydronephrosis, bilateral. Hydroureter, bilateral.

"The external wound gapes widely and is filled with an exuberant growth of soft dirty brownish granulations flecked with brownish black spots. On opening the peritoneal cavity it is seen that the floor of the right iliac fossa bulges forward. The peritoneum covering it is thickened and gives a sense of fluctuation. The small intestine is moderately contracted and the coils of the ilium in the lesser pelvis are matted together by dense adhesions. An incision through the posterior peritoneum showed the fluctuant mass to consist of jelly-like yellowish material containing innumerable brownish granules the size of millet seeds. This extends inside the space of Retzius and posterior to the bladder beneath the peritoneum nearly to the midline. At this point the coils of the small intestine are matted together by dense adhesions. When they are separate an abscess cavity measuring about 5 x 5 x 1 cm., irregular in shape, is found containing greenish pus and completely walled off. The mass extends upward to the lower pole of the right kidney, which is normal in position. The tip of this pole is invaded by several nodules of soft yellowish tissue. The right sides of the second, third, fourth and fifth lumbar vertebræ are softened and black to a depth of a centimeter. The surface of the right iliac bone is bare in many places and is eroded, forming small pit-like depressions from one to several centimeters in diameter. The growth extends into Scarpa's triangle and the finger can be passed around the medial side of the femur below this.

"One or two lymph nodes in the right groin and one or two retroperitoneal nodes in front of the lumbar vertebræ are slightly enlarged, firm, and show yellowish tissue in the central portions.

"In the inferior vena cava is an adherent thrombus extending from just beyond the bifurcation upward four inches. This is about 5 mm. broad, 3 mm. thick, is yellowish and quite firm. It is smooth in some parts, granular in others and is firmly attached to the vessel wall.

"The mucosa of the bladder is diffusely reddened and over an area 2 cm. in diameter on the left side posteriorly it is roughened and black. At this site the matted coils of the intestine are adherent to the bladder.

"On section the lungs are pale red and are well aerated except in certain parts where the tissue is dark red, granular, and firm, and centrally is softened and brownish. These central areas have a foul odor and the degree of softening varies. The largest of these areas has a spongy necrotic center and the branch of the pulmonary artery leading to it is found to contain a firm yellowish thrombus lodged at the bifurcation with a prolongation running down into each branch. It is quite firmly lodged to the wall at the bifurcation.

"Microscopically the retroperitoneal tissue shows typical ray fungi in large numbers. They are immediately surrounded by polynuclear leucocytes and at a greater distance by vascular granulation tissue in which fibroblasts, plasma cells and lymphocytes are the predominating cells. A section of the lower pole of the right kidney shows typical ray fungi and in the wall of the inferior vena cava at the site of the thrombus there are typical ray fungi."

The second case is also that of a male negro. This man was twenty-five years old and had recently come from Panama. His occupation is not known. He was in coma when admitted to Bellevue and died a few hours later. The only history obtained was that he had recently come from Panama. Because his signs were obscure and his history unknown he became a case for the medical examiners of the city. A necropsy was performed by the Assistant Medical Examiner, Dr. Benjamin Schwartz, and I am indebted to him and to Chief Medical Examiner, Dr. Norris, for permission to present this case.

The necropsy demonstrated a bronchopneumonia and certain lesions in the liver, the ilium, the appendix and the colon as described below.

The liver was enlarged and was unusually adherent to the diaphragm. It was normal in color externally but the surface was bulging in one or two rounded areas. On section the parenchyma was found to be much reduced and there were present multiple abscesses varying in size from that of a pin head to one that was the size of an orange. These abscess cavities were lined by firm fibrous tissue. In some areas numerous smaller cavities had coalesced into one making the appearance that of a unique alveolar or honeycombed structure like "a sponge soaked in pus" to use Rolleston's description of a similar lesion. The lining tissue had a faintly yellowish tint. The pus from the abscesses was thick and viscid and yellowish-green in color. No granules were observed on casual examination. A methylene-blue stained smear revealed no typical picture although there were seen numerous homogeneous rounded bodies with suggestive feathery edges.

The wall of the colon was thickened and in places quite nodular. The mucosa presented numerous irregularly placed superficial round and oval ulcers not over 1 cm. in diameter. These apparently involved only the mucosa

and to a slight extent the submucosa. The edges were not raised or undermined and the ulcers were not typical of tuberculosis, typhoid fever or amœbic dysentery.

Externally the appendix, ilium and cecum were normal and their mucous surfaces showed nothing unusual.

Because a stained smear of the pus had been negative and because of the general characteristics of the lesions, together with the fact that the patient had recently come from Panama, a tentative diagnosis was made of amœbic abscesses and ulcers with actinomycosis to be ruled out microscopically.

Routine sections revealed typical ray fungi and no evidence of amœbic abscesses. The appendix was then sectioned serially and in the submucosa and muscularis was found an abscess extending longitudinally for a distance of about half the organ. No defect in the mucosa was demonstrated and the serosa was intact. The abscess appeared yellowish and granular with thin fibrous trabeculæ throughout. A similar abscess was discovered in the wall of the terminal ilium but gross serial sections of the colon did not reveal abscesses. Microscopical sections revealed typical ray fungi in the wall of the appendix and in the ilium. No ray fungi were found in sections of the wall of the colon. The possibility of the lesions in the colon being due to the actinomyces is greater because of the similarity between these lesions and those in a case described by Chiari [2, 32] who says that primary actinomycosis of the intestinal tract manifests itself as a superficial invasion of the mucous membrane in the formation of whitish patches or in the more diffuse variety by the formation of nodules beneath the mucosa. These nodules undergo degeneration, ulcerate and rapidly extend. However since no ray fungi were demonstrated in the wall of the colon a diagnosis of actinomycosis of the colon can not be made.

Pus had been saved from this case and a more careful examination revealed characteristic granules. A majority of these were like sand grains in size and color. Some, however, were dark brown and some were sulphur yellow. All were soft. When some of this pus was shaken in a test tube of normal saline the grains were easily isolated from the viscid suspension and could be demonstrated clinging to the sides of the tube. Granules pressed between a cover slip and slide presented microscopically typical unstained mycelia. An anaerobic culture in dextrose agar had been made at the time of necropsy and a growth of *actinomyces bovis* was isolated.

In this case the primary lesion may very likely have been in the appendix if we accept the views of many observers. If so the fungi traveled via the blood stream to the liver.

The case illustrates the possibility of missing a correct diagnosis without particular care and special methods of examination. Pus in suspected cases should always be examined carefully for granules for it is very easy to fail to see them. The simplest method is to shake a small amount of the pus in a test tube of

water or normal saline. Having isolated a granule, it may be pressed between two glass surfaces and examined microscopically. Typical mycelia may readily be identified. Clubs will rarely be present in the human cases. A methylene-blue and a Gram stain will further aid in the diagnosis, but are confusing if applied to a smear of pus rather than to an individual granule that has been washed in saline. It should be remembered that the granules are by no means always the typical sulphur granules of the text-books. On investigation of the literature the following color designations were found applied to the granules: white,[5] pearly white,[1] grayish white,[7] yellowish white,[1] black,[8] brownish black,[7] brown,[9] gray,[10] pearly gray,[1] yellow gray,[11] cream colored,[12] red,[13] yellow,[14] sulphur yellow,[15] lemon yellow,[11] whitish yellow,[15] green.[7]

The granules have been described as granules, grains, specks,[8] like sand,[13] like minute pearls, like minute raspberries,[9] like fish roe,[14] like gun-powder,[8] like rice particles,[16] and they may be soft, firm or calcific.

The color of the pus has been described as white, cream, yellow, chocolate, and green.

Routine sections of tissue were stained with hematoxylin and eosin. Mr. Wm. Johnson, technicist in the Bellevue laboratories, prepared other sections stained with carbol fuchsin, then decolorized and counterstained with picric acid. In these the ray fungus stands out as a red aster on a yellow background.

In none of the sections from the two cases presented were ray fungi seen with typical clubs. A typical actinomyces rosette is made up first of a central felt-like core of long, thin, branching filaments irregularly disposed but with a general radial arrangement and not decolorized in the Gram method of staining. Secondly, there may be at the periphery of the central core a crown of pear-shaped swellings of the terminal ends of the filaments. These are Gram-negative. Hiss and Zinsser[44] believe that they represent a form of degeneration and that they are the hyaline thickened sheaths of the threads. They are more frequently absent than present in the rosettes from man but are nearly always present in those from cattle. Thirdly, there have been described

coccus-like bodies that resemble spores and that led to the classification of the actinomyces as a spore-bearer. They are not spores, however, according to modern workers, but are either symbiotic cocci or else degeneration products.

Although the fungi in these cases did not show the clubs, they were typical in all other respects.

*Conclusions:*

In conclusion it may be noted that the chief problems in the study of actinomycosis are first as regards the method of infection and secondly as regards the method of treatment. Neither of these phases of the disease has been satisfactorily dealt with. Where the fungus is when not actively invading the tissues, how it gets into these tissues, whether it is a normal inhabitant of the various tracts of the body, whether it hides away in tonsils and dead teeth, all of these questions are as yet unanswered although there are many more or less attractive theories to explain them.

Finally, it should be emphasized that in every chronic suppurative lesion resembling tuberculosis, syphilis or a neoplasm, actinomycosis should if possible be carefully ruled out. This is especially true of atypical pulmonary disease where repeated sputum examinations should be made with a view to finding the ray fungus in the absence of the tubercle bacillus.

The diagnosis of actinomycosis is never established until typical ray fungi have been demonstrated. These may be found in tissue, in pus, in sputum, in urine, in feces, in spinal fluid, and most rarely in blood.

*Discussion:*

DR. HAAS: I happen to have at the present time a case of intestinal actinomycosis in a young man of twenty-one. He is dying now. The onset was almost identical to that of the case Dr. Russell described. He was first seen about two and a half years ago, when he gave a history of some abdominal distress during the previous week, and on the day of onset sharp pain in right iliac with nausea. When examined there was moderate shock, with a temperature of 100.5°. There was slight rigidity and tenderness of the right iliac region, and I decided it was probably appendicitis. Dr. Elsberg was called and that evening the boy was operated on. There was no inflammation of

the appendix, but the ilium near the appendix showed a perforating ulcer which was covered by omentum. There was some free sero-pus in the abdomen. At that time neither of us had any suspicion of what it was. Everything went along very well for a number of days, when after a rise of temperature a fecal fistula formed. This resisted all methods of treatment, and soon the subcutaneous tissue around the wound disappeared, and the skin with it, and there was an area about as big as the palm of the hand which was entirely exposed. At this time search was begun for the fungus, the differential diagnosis lying between syphilis, tuberculosis and actinomycosis. Nothing was found corroborative of any of these diagnoses. This condition continued for a long time, and it was then decided to remove the sinus. A second operation was performed and the sinus excised widely, and it seemed as though the result would be good. The wound healed very well, and just as the boy was to be discharged, the wound perforated, and the previous experience was repeated. As a matter of fact the fungus was not found until pus from a freshly perforating sinus was obtained. The boy now has five sinuses in his abdominal wall. It is only at the moment of perforation that one is able to find the fungus. Even after the character of the infection was known, examination of the pus failed to show the fungus again. The patient is now having very violent back-aches so that the vertebræ are perhaps becoming involved. So far as therapy is concerned, neosalvarsan, large doses of potassium iodide, methylene blue and emetine have been given, and as a last resort radium was tried, and that just about finished him. It was very interesting indeed to see how that treatment accelerated and intensified the progress of the disease. We have seen the same thing occur when the x-ray was used therapeutically in pulmonary carcinoma, the treatment producing intense toxemia and death within a short time.

DR. MOSCHCOWITZ: Actinomycosis is not as rare if you look for it. I have seen a considerable number of cases—a few of them in the lung, a very few in the abdomen, and a good many in the skin and bones. There is one point in connection with the diagnosis of actinomycosis which is emphasized by Dr. Libman, and that is that tenderness is a prominent symptom. We all know that the prognosis is bad. We hardly realize how bad it is. I have seen a number of patients in whom the lesion is apparently healed, and in whom months or years later either the wound breaks down, or a focus appears in another part of the body.

DR. RUSSELL: In regard to the frequency of actinomycosis observers differ. Dr. Moschcowitz, for example, states that he has seen a considerable number of cases and believes that the disease is not rare. On the other hand some observers have encountered it but rarely. Griffith [45] for example reports two cases as the only ones he has seen in fifteen years of active practice. He believes that the disease is rare and states that his colleagues have the same opinion.

In Bellevue as recorded above there have been only five cases in fifteen years. In the records of Roosevelt Hospital there is listed only one case. At New York Hospital there are only three cases in the records. At Bellevue

two cases have been autopsied in fifteen years; none have been autopsied at either Roosevelt or New York Hospital.

Undoubtedly cases are missed clinically but since all diseased tissues are sectioned at the post mortem table and a careful microscopical study made, it does not seem probable that many cases are missed that come to necropsy.

As to the frequency with which different parts of the body are involved there have been a number of reports. Ruhrah [16] in his first report had collected 632 cases throughout the world and reported actinomycosis primary or maximum in

| | Per Cent. |
|---|---|
| Head and Neck | 57 |
| Gastro-intestinal Tract | 21 |
| Thorax | 15 |
| Skin | 2 |
| Doubtful | 5 |

Later he [16] had collected 1,094 cases with practically no change in the above percentages.

Taking the reports of six series of cases the following averages are obtained:

| | Per Cent. |
|---|---|
| Face and Neck | 55 |
| Abdomen | 23 |
| Thorax | 17 |
| Skin | 5 |

In regard to the frequency with which the various organs are involved in the first place it may be noted that practically every organ in the body has been attacked by the ray fungus. But in abdominal cases the appendix and the cecum seem to be the site of election. Hinglais [17] found the appendix involved in 60 per cent. of his cases. Kelley [18] and Cope [19] state that the appendix is the commonest site of infection, while Waring,[20] who reports seven cases, believes that the cecum is the commonest site.

Actinomycosis of the liver, according to Rolleston,[4] is rare. He states that Auvray in 1903 could collect only thirty-one cases.

Secondary actinomycosis of the kidney has been repeatedly observed. Garceau [21] for example reports 128 autopsies collected from various sources in which there was actinomycosis somewhere in the body and in eleven of these cases the kidney was involved. According to Ransohoff [22] the only case of primary actinomycosis of the kidney was reported by Israel. In this case the organisms were identified in the urine and in pus from a lumbar fistula.

Robinson [23] in 1919 collected nineteen cases of actinomycosis of the female genitalia, reporting a case in which he found it in both ovaries in a patient fifteen years old.

Hodenpyle [24] collected thirty-four cases of pulmonary actinomycosis, and Hichens [33] gives a good account of this form of the disease.

The heart may be affected by metastases or by continuity.[25]

Actinomycosis of the brain has been reported, but it is rare.[27]

Cases have been reported involving the stomach,[34] gall bladder,[35] breast,[36] tongue,[37] larynx,[38] skin,[16, 39] retina,[40] conjunctiva,[41] salivary gland [42] and elsewhere.

As both Dr. Haas and Dr. Moschcowitz have observed, the course of actinomycosis is chronic. It is not infrequently recorded that after an apparently successful appendectomy, the patient, having been discharged as cured, will in the course of a few months to a year return with a draining wound or an abscess, and at this time a second operation and more careful examination will disclose the organism of actinomycosis in the pus.

The mortality is fearful. In Keen's surgery the mortality from all cases is given as 47 per cent. Frazier [2] says the mortality in cases of abdominal actinomycosis in the United States has been 71 per cent.

Jiron [2] gives the following mortality statistics:

| | Per Cent. |
|---|---|
| Cerebral | 100 |
| Thoracic | 83 |
| Abdominal | 71 |
| Face and Neck | 11 |

So far no satisfactory treatment has been devised as the above mortality statistics demonstrate. Consequently every observer who has had two or more cases has experimented along lines of his own devising.

Potassium iodide is mentioned in all text-books but it has never been shown that there is the slightest scientific basis for the use of this drug which was introduced empirically by Thomassen [29] in 1885 for actinomycosis of the tongue in cattle and which was later proclaimed by Nocard [12] to be specific.

Harbitz and Gröndahl [7] have demonstrated that the *actinomyces bovis* will grow luxuriantly on potassium iodide media in which the iodide is present in from 0.25 to 2 per cent. concentrations. Logically they doubt the value of this drug in the disease.

In fact potassium iodide may even be harmful. Jobling and Peterson [30] believe as a result of their experiments that the iodide neutralizes the action of the agents which prevent the solution and absorption of necrotic tissue and at the same time therefore lays bare to the action of the real germicidal agent the infecting organism that has been protected by the necrotic tissue. If this is true potassium iodide may accelerate this disease, for there is no known germicidal agent that can be administered to destroy the actinomyces in the tissues. Hence the organism may be speeded in its journey to other parts of the body.

Bevan [43] tried copper sulphate on the theory that it is effectual against vegetable parasites and he has had some success with it. Later he recommended using both potassium iodide and copper sulphate.

Many other drugs have been tried with occasional cures.

Autogenous and stock vaccines have been used.

X-ray and radium have been of some value apparently in a few cases. Heyerdahl [31] reports six cases of cervico-facial actinomycosis cured by radium.

But in most of the series reported where various methods have been used the mortality has been in accordance with the average figures as given above, no matter what the treatment. For example Colebrook[12] advocates surgery plus vaccines. In his series, nine out of eleven cervico-facial cases were cured, all six of his thoracic cases died, and five out of the six abdominal cases died.

There is no doubt that effectual drainage should be established, but as to the medical and mechanical treatment beyond this there is confusion.

*Bibliography*


1. Erving: *Bull. Johns Hopkins Hosp.*, 1902, xiii, 261.
2. Frazier: *Keen's Surgery*, Vol. 1, p. 524.
3. Norris and Landis: *Diseases of the Chest*, 1917, p. 381.
4. Rolleston: *Diseases of the Liver*, 1916, p. 381.
5. Wright: Osler and McCrae's *System of Medicine*, 1913, p. 1033.
6. Wright: *Reference Handbook of Medical Sciences*, 1913, Vol. 1, p. 104.
7. Harbitz and Gröndahl: *Am. Jour. Med. Sc.*, 1911, cxlii, 386.
8. French: *Differential Diagnosis*, 1920, p. 677.
9. Achard: *Albutt's System of Medicine*, 1912, Vol. 2, part 1, p. 324.
10. Lord: *Oxford Loose-Leaf Medicine*, 1920, Vol. 5, p. 397.
11. MacLeod: *Diseases of the Skin*, 1920, p. 431.
12. Colebrook: *Lancet, London*, 1921, 1, 893.
13. Stengel and Fox: *A Text-Book of Pathology*, 1921, p. 518.
14. Sutton: *Tice's Practice of Medicine*, 1920, Vol. 4, p. 119.
15. Barker: *Monographic Medicine*, p. 326.
16. Oertel: *General Pathology*, 1921, p. 72.
17. Murphy: *Keen's Surgery*, Vol. 6, p. 573; Vol. 4, p. 760.
18. Kelly: *Appendicitis*, 1909.
19. Cope: *Brit. Jour. Surg.*, 1915–16, iii, 55.
20. Waring: *St. Bartholomew's Hospital Report*, 1905, p. 197.
21. Garceau: *Tumors of the Kidney*, 1909, p. 307.
22. Ransohoff: *Keen's Surgery*, Vol. 4, p. 233.
23. Robinson: *Surg., Gynec., and Obst.*, 1919, xxix, 569.
24. Hodenpyl: *New York Med. Jour.*, 1890, Dec. 13.
25. Letulle and Hufnagel: *Bull. de l'Acad. de Med., Par.*, 1919, lxxxii, 120
26. Howard: *Jour. Med. Research*, 1903, ix, 301.
27. Vollinger: *München. med. Wchnschr.*, 1887, No. 41, p. 789.
28. Enriquez and Sicard: *Lancet, London*, 1904, June 4, p. 1585.
29. Thomassen: *L'Echo Vet*, 1885.
30. Jobling and Peterson: *Arch. Int. Med.*, 1915, xv, 286.
31. Heyerdahl: *Jour. Am. Med. Assn.*, 1919, lxxiii, 1928.
32. Chiari: *Prag. med. Wchnschr.*, 1884.
33. Hitchins: *Brit. Med. Jour.*, 1905, Nov. 4.
34. Robson: *Keen's Surgery*, Vol. iv, 478.
35. Robson: *Diseases of Gall Bladder*. Ed. 3d, p. 173.
36. Furiez: *Keen's Surgery*, Vol. iii, p. 574.

37. Binnie: *Ibid.*, Vol. ii, p. 442.
38. Brewer: *Ibid.*, Vol. iii, p. 543.
39. Pels: *Jour. Cutan. Dis.*, 1919, xxxvii, 740.
40. Mueller: *Klin. Monatsbl. f. Augenh.*, March, 1903.
41. Brunetiere: *Jour. de Med. de Bordeaux*, 1920, xci, 459.
42. Söderlund: *Acta chir. Scandinav.*, 1921, liii, 189.
43. Bevan: *Jour. Am. Med. Assn.*, 1905, xlv, 1492.
44. Hiss and Zinsser: *Text-Book of Bacteriology*, 1918, p. 623.
45. Griffith: *Surg., Gynec., and Obst.*, 1921, xxxiii, 5.

---

# ENDOCRINE GLAND STUDIES, INCLUDING GOITRE IN INDIA*

ROBERT MCCARRISON, M.D., F.R.C.P., LT.-COL.

*Indian Medical Service*

I desire in the first place to thank you for the honor you have done me, and the Service to which I belong, in inviting me to speak to you this evening. I see in this audience so many whose researches have made their names familiar to students of endocrine disorder that it is with a certain diffidence I bring before you the results of my own investigations, carried out for the most part in the far distant Himalayas.

It is now some twenty years since Fate sent me to a part of the world where goitre was extremely common. I found myself, in 1902, posted as agency surgeon in hill stations situated in the Hindu-Khush region of Northern India, first in Chitral and later in Gilgit. The nearest railroad station is at Rawalpindi, some twenty days' journey by tonga, boat, horse and mule from Gilgit. One has, therefore, some excuse for speaking of one's work as having been done under isolated conditions. The facilities for intercourse with one's fellow-workers were, of course, very limited indeed; while access to medical literature was very restricted.

In Chitral and Gilgit goitre was so common that in some vil-

* Stenographer's report of a lantern slide demonstration given before the New York Pathological Society on November 9, 1921.

lages no one was free from it. In localities where its endemicity was high, men, women, and children alike suffered from it. In the village of Awi in Chitral, for instance, about sixty per cent. of the children were born with congenital goitre, while many were cretinous, and every man, woman and child was goitrous. The villagers used to say of this village that "even the trees had goitre"; there was some excuse for their thinking so, since many of the trees did have curious nodular growths on their barks. These excrescences arose, of course, from causes other than those which gave rise to goitre. The goitrous state of this village, which was not exceptional, gives an idea of the extent of the prevalence of the disease and of its congenital manifestations. But while it was so prevalent as this in one village, another situated, it might be, within pistol-shot of the first might have no goitre at all. This circumscribed distribution of endemic goitre has always been a very great puzzle.

When I first went to Chitral in 1902 most of the current views as to the causation of goitre centered around the water-supply; it was thought to be due to excess of lime or of magnesium in the water, or to be due to snow water. So knowing nothing, premising nothing, I began to occupy myself in the study of its etiology. The first observation of any importance which I made was as follows: There were on the Gilgit-Fan eight villages situated one above another on a single water supply. I made a survey of the endemicity of goitre in each of these villages. Every man, woman, and child was examined. It was found that in the first village there was eleven per cent. with goitre. The water was not confined to the banks of the stream, but was used to irrigate the cultivated land between the villages. The irrigation water joined the main stream at the second village, and in this village the percentage of goitre had risen to eighteen. The stream spread over the fields, irrigating them, and came to the third village where the incidence of goitre was twenty per cent. Below this point the main stream was joined by another of exceptional purity, and the fourth village showed a drop in the incidence of goitre to eighteen per cent. I need not continue with this de-

tailed description, but I will tell you that the incidence of goitre gradually increased until ultimately it reached forty-five per cent. in the eighth and lowest village on the common water-supply. This observation was made in 1906. Later Dr. David Marine, than whom there is no one who has contributed more to our knowledge of thyroid disease, made a similar observation with regard to artificially bred trout. He found that goitre gradually increased from above downwards in the tanks holding the trout, and that a diminution in the incidence of goitre occurred when the stream was joined by another water-supply. Since then I have pursued one line of investigation and Dr. Marine another, but to-day finds us in substantial agreement. I took the line that the increasing incidence of goitre in villages situated one above another on the same water-supply was associated with the increasing bacteriological impurity of the water. I thought that if this were the case, and if bacteria were concerned in the production of goitre, then the disease might be curable by intestinal antiseptics. Consequently, a man who had a well-marked goitre without adenomatous degeneration was given large doses of salol. After he had been taking salol for ten days or so and no appreciable improvement had been noted, I went on tour, leaving him still on salol. At the end of six weeks, I returned and found his goitre had disappeared. I then tried thymol in other cases, using the drug in large doses, and I got results with this drug which I will presently show you on the screen; they justified my assumption that bacteria in the digestive tract were concerned in the genesis of goitre.

Before I go on I wish to say a word or two about the goitres which one found in Chitral and Gilgit. In the first place, Graves' disease, or exophthalmic goitre, was practically unknown. I can count on the fingers of one hand the cases of Graves' disease which I saw among the indigenous inhabitants of Gilgit; and when one is dealing in thousands of cases of goitre that is a very striking thing. The cases of Graves' disease which I did see were definitely associated with fright or shock. Another point which I wish to make is this, that throughout India Graves' disease occurs

but rarely amongst the indigenous inhabitants. Some three or four years ago I sent a request to the great Presidency hospitals in India—at Calcutta, Bombay, and Madras—where the number of patients coming to the hospital in a year is very large, asking the superintendents to let me know the numbers of cases of Graves' disease admitted amongst various races of India during a period of ten years. They sent me figures which showed that it was very rarely found among the indigenous inhabitants, although it did occur amongst those who were strangers to the land—Europeans, Parsees—and was also comparatively common among Anglo-Indians. During the war, however, I came across a number of cases of Graves' disease among Indian troops who had been to Europe. It is a point of considerable interest that among men who had come from India, where Graves' disease is practically unknown, examples of this malady should have been encountered. It would seem that the conditions of service in Europe were such as to favor its development in Indians, who in their own country are rarely affected by it. I throw out the suggestion, therefore, that Graves' disease is a disease of civilization. Another point is this: almost all cases of goitre of long standing in Gilgit ultimately become adenomatous, and yet I never saw hyperthyroidism associated with thyroid adenoma. One reads a very great deal about "toxic adenoma." I have never seen it in the Himalayas.

With your permission I will now show you some slides. This one represents a goitrous patient who was the first man I ever treated with thymol. He looked after a herd of cattle and continued this occupation throughout the whole course of treatment. He came regularly to hospital for three and a half months. He had a goitre which caused the circumference of his neck to measure 42 cm. The next picture shows the same man after three and a half months' treatment by thymol, when his neck measured 36.5 cm. There is no doubt about the result. The man did his customary work; he was not a resident patient in the hospital, and to my knowledge he did not get any other treatment. I collected many more such cases. Messereli of Lusanne has pub-

lished many cases confirmatory of this action of intestinal antiseptics in recent cases of endemic goitre.

Now came the next step. I assumed, if I were dealing with intestinal organisms having to do with the causation of goitre, that I might get results by preparing vaccines from them, and treating recent goitres with such vaccines. Here is a picture of a man with goitre that had caused the circumference of his neck to measure 42 cm. before vaccine treatment was commenced. I gave him an autogenous *B. coli* vaccine in large doses once a week. Within a few weeks the goitre had disappeared. In those days my methods of standardizing vaccines were not so accurate as they would be to-day. I was probably giving this man much larger doses than I thought. He, as well as others similarly treated, had marked reactions after the injections. Here is another man who was treated by vaccines. This case is interesting, because the vaccine with which he was treated was made from a spore-bearing organism obtained from the fecal discharges of one of my polo ponies that had developed goitre. I injected it into this man in large doses. He was so greatly improved after several weeks' treatment as to show little trace of his goitre. These results were obtained with vaccines made from various intestinal bacteria. There was no specificity about their action.

I have shown you three or four of these cases, and I think you will have observed from the pictures that apart from the improvement in the goitre itself, the general appearance of the patients greatly improved. Any hypothyroidism which they may have had cleared up. The skin became much finer and softer, and the face thinner and less puffy looking,—a result noted also to follow cure by iodine, by thyroid extract, by soured milk, or by intestinal antiseptics. Precisely how large doses of vaccines may bring about this result, or what component of the bacteria is responsible for it, I do not know.

The next step in my work was to see whether I could induce goitre in man and animals. I have made a great number of attempts to do so. This picture shows the trachea with the attached

thyroids of a number of rats. The top row shows those of the control white rats. The second row shows the thyroids of wild rats from the locality in which the experiment was conducted. So you will see that the white rats did not have any goitre when the experiment was started. I got a large cage and divided it into three compartments of equal size; in each I put six white rats. In one compartment were the controls. In the second were rats which were fed on the residue left on the candle of a Berkefeld filter after filtration of a fecal emulsion from a goitrous person. In the third were rats which received the fecal filtrate. One hundred per cent. of the animals which received the fecal material developed goitre while the controls on the same food and in the same cage did not. The result of this experiment strengthened me in my assumption, which was becoming a belief, that goitre in Gilgit was intimately associated in its origin with bacterial organisms resident in the alimentary tract, and reaching the tract by way of water or contaminated food. At that time I only thought of such organisms as contributors of positive agents to the thyroid's harm. I could not think of them apart from the direct action of their toxins, so I believed for a time that goitre was caused by the direct action of microorganisms or of their toxins on the thyroid gland, and I continued my search for a specific bacterial excitant of the malady. I have altered that view to some extent; and have abandoned the view of a specific bacterial excitant, while still maintaining my position as to the important relation that exists between bacterial agents and the genesis of goitre and of thyroid disease in general.

Before starting these experimental investigations on a large scale, I had to establish a base line of normality for the thyroid gland of the animals (rats) with which I was working, because most animals kept in confinement showed some degree of thyroid change. What I did was to ask the plague medical officers to send me a large number of the rats which they caught in connection with anti-plague measures. They sent me some six hundred wild rats from various parts of India. I found some interesting things in connection with these rats. In those from the sea-coast

and from about the level of the sea-coast, the thyroid had in the majority of cases the appearance shown on the screen: the acini were well defined and distended with colloid, low cuboidal or flattened epithelium lined each acinus, and the organ was in its colloid or resting phase. On the other hand, a number of them were like this. The vesicles were smaller, the colloid was much thinner and less plentiful, the acinar cells were higher, and the gland was in a condition of physiologically active secretion. About twenty-five per cent. coming from the sea-level were of the latter type. When I examined the thyroids of rats from localities at a height of six thousand feet or more above sea-level, the greater proportion of them were found to be of the second type, that is to say, of a type which one associates with greater physiological activity. It seemed, indeed, that the farther from the sea-coast or the higher the altitude, the more physiologically active was the thyroid, an observation that may not be without significance in connection with the preference of goitre for mountain ranges.

The next specimen is a section of an experimentally produced goitre in a rat; you will see that there is evidence of marked hyperplasia; the amount of colloid is very small; the acinar cells are high; there is a tendency to acinar budding, and the thyroid is beginning to assume the histological characters which it is customary to connect with Graves' disease.

The next step in my inquiry was to see if I could produce cretinism and other congenital manifestations of thyroid defect; so I fed rats throughout pregnancy on fecal material or on bacterial cultures from the feces of goitrous persons. Here is a litter of three young rats aged twenty days. The mother of these animals was fed on milk and unleavened bread, and received the fecal filtrate from an emulsion of feces. The middle one is very much smaller than the rest. It has curvature of the spine and is but sparingly clothed with hair. After I had photographed this litter, the badly grown animal in the center was eaten by its parents. In order to avoid that risk in future I killed the young that were born to mothers fed on fecal material, four days after birth. This specimen shows a four-day-old litter, one of which is a cretin.

This is its thyroid and parathyroid glands. The gland was devoid of thyroid structure and was made up largely of connective tissue cells; the thyroid apparatus was congenitally atrophic and there was no evidence of vesicle formation nor of colloid. It was thus shown that there was something in the fecal material from goitrous persons which when administered throughout pregnancy to goitrous rats was capable of causing cretinism in the young.

The next specimen shows the effect of fecal anaerobes when fed to pregnant rats in causing hemorrhagic lesions on the parathyroid glands. I found such lesions as these in quite a high proportion of newborn rats whose mothers had received, throughout pregnancy, anaerobic cultures of fecal bacteria in glucose broth.

After dealing with rats I went on to larger animals. I procured from Delhi a number of female goats of the first year that had never had offspring. They were brought up to my laboratory, which was situated at a height of 6,900 feet above sea-level. Eight were kept as controls, and twelve were used for the actual experiment. Both controls and experimental animals received the same food; there was no difference in their intake of iodine. The only difference was that I muzzled a number of my controls so that they could not eat anything except what I gave them. I fed these goats for several months on cultures of fecal bacteria. On one day they received 10 c.c. of a 24–hour culture in 2 per cent. glucose broth, on the next a 48-hour culture, on the third a 72–hour culture, on the fourth a 24–hour culture, and so on. After several months the thyroids of most of them were palpable. They were then impregnated, and during pregnancy these cultures were continued. They gave birth to young that were all dead-born, hairless, and having enormous goitres. The controls on the other hand which received no cultures gave birth to kids that were fully developed and had excellent coats. Several among the control kids had small congenital goitres which disappeared shortly after birth and one was born dead but fully developed. The contrast was so great that it is impossible to escape the conclusion that the cultures referred to contained bacteria or their

products that greatly favored the development of congenital goitre and cretinism.

At one stage of the proceedings I took water from the last village on the Gilgit water-supply and passed it through the candle of a Berkefeld filter. Sixteen young men, including myself, drank, night and morning, under strictly controlled conditions, a cupful of the residue left on the candle of the filter. I had no medical colleague who could check my investigations, so I was forced to rely on a member of another profession—an engineer. I thought he would probably be capable of noticing any changes in the size of our necks. He measured my neck before the experiment commenced and after it was completed. At the end of the experiment he gave me a certificate which I came across among a lot of old records a short time ago. It said that I had a swelling on the right side of my neck, and a bridge of tissue across the windpipe that rose and fell on swallowing, and that neither of these were there two months before. So I think you can take it that I did have a goitre, as did also several of the others. The controls remained goitre-free.

Having thus produced goitre in man and in animals; having also produced the effects of thyroid deficiency in the offspring; and having cured goitre by intestinal antiseptics and by vaccines, the next step was to prevent it on a large scale. The opportunity presented itself when, in 1913, I was asked to report on a school just below Simla where goitre was extremely prevalent. This school is intended for the boys and girls of British soldiers who cannot be sent home to England for their education. They get an excellent education there, but unfortunately they suffered greatly from goitre. You will see from the chart which I now show you that among boys between five and ten years of age something like eight per cent. were goitrous. Among boys of sixteen and over, forty-three per cent. were goitrous. Among the girls the incidence of goitre was even more marked. In those between ten and fifteen years of age fifty-nine per cent. were goitrous, while sixty-four per cent. of the girls over sixteen were goitrous. This state of affairs was very serious, especially when

one knew, as I did then, that approximately five per cent. of all goitrous mothers give birth to cretinoid children. The boys and girls were in separate parts of the school; it was convenient to use the boys for the purpose which I had in view. I thought, after a study of the site and the water-supply, that the disease might be due to fecal pollution of the water; bacteriological examination every day over a long period showed it to be badly contaminated. Consequently I began to purify the water, using Nesfield's reagent which contains iodine. I used this reagent for about seventy-five days. After that I used chlorine. The water given to the boys was treated in this way. That given to the girls was not so treated. After six and a half months there was a drop from forty-three to twenty-four per cent. in the cases among boys, whereas among the girls, where the water was not treated in this way, there was a rise in the incidence of goitre. We reported on this observation, emphasized the beneficial effect of these reagents in the purification of the water as a means of preventing the disease, and recommended the continued use of chlorine as a purifying agent, or the introduction of another water-supply. It was ultimately decided to follow the latter suggestion. It may be that I laid too little stress on the specific effect of the iodine on the thyroid gland as an essential factor in reducing the incidence of goitre in this school. I have no doubt that a part of the good effect was due to the specific action of iodine, but equally no doubt that the removal of the bacterial impurity of the water was also concerned in bringing it about, for when a new water-supply was introduced the disease gradually disappeared. I have lately been officially informed that at the present time goitre is no longer prevalent in this school. The evidence that fecal pollution of the water had to do with the presence of goitre in this school is very strong. Dr. Marine's work, with which you are all familiar, shows the ease with which this very insidious disease can be eradicated by the prophylactic use of iodine. But this does not mean that the bacterial factor in its causation can be ignored, for it would seem that in the presence of certain bacteria in the alimentary tract more iodine is needed to

insure healthy thyroid action. The prophylactic use of iodine is a measure of the utmost importance. Anyone who has seen the moral and physical degeneration which can result from goitre must realize what a tremendously important thing it is that goitre should be prevented. We cannot as physicians emphasize too strongly the very great importance of preventing this disease in localities where prevention can be undertaken. It is a measure of the highest national importance in all countries where endemic goitre prevails.

We have then two important facts relative to the genesis of endemic goitre: first, that bacteria in the alimentary tract can be concerned in its genesis, and second, that small amounts of iodine will prevent it—extraordinarily small amounts. There must be some connection between these two facts. The ultimate cause of goitre is of course the undue stimulation of the thyroid gland consequent on the insufficient supply of iodine. I now think that this supply may be interfered with in a number of different ways: by insufficient intake of iodine, which is comparatively rare; by imperfect absorption of iodine; by insufficient assimilation of iodine; or by its imperfect utilization by the thyroid gland. It is within the orbit of these possibilities that we must seek for the true explanation of the influence of bacterial agents. It is to be remembered that goitre can and does arise in many cases where the provision of iodine is inadequate. Bacterial agents may act by preventing, in some way, the absorption, or by interfering with the assimilation of iodine, or by impairing the utilization of iodine by the thyroid gland.

The next part of my address will provide additional matter for consideration in this regard, and bring into prominence nutritional factors in thyroid disturbance. I wish now to show you some of my more recent work on the effects of faulty foods on the thyroid gland. This picture shows the normal thyroid gland of a monkey; contrast it with the next which shows the thyroid gland of another monkey that was fed for a considerable time on a diet of autoclaved rice and butter, that is to say, on a diet which is deficient in vitamins B and C, and disproportionately rich in

starch and in fat. The vesicles are small, the colloid is thin, and there is a great deal of congestion. The dark areas around the alveoli are distended blood spaces. That is an effect which I have noticed in a high proportion of animals fed in this particular way.

The next picture shows the normal parathyroid gland of a monkey. I wish you to contrast it with this which shows the intense congestion of this organ that is brought about as the result of a food deficient in vitamins and ill-balanced in other respects. You will remember that hemorrhagic lesions of the parathyroids can be produced in newborn rats by feeding their mothers during pregnancy on anaerobic cultures of fecal bacteria. Here is a similar result, but brought about by faulty food. It would seem almost as if the deficient food had enabled anaerobic microorganisms to exert their harmful effect on the parathyroid glands.

This chart indicates that the endocrine organs, with the exception of the adrenal glands and the pituitary body, undergo atrophy in consequence of a diet deficient in vitamins. The adrenal glands enlarge, and the enlargement occurs both in inanition and in that form of starvation which is known as avitaminosis. This dark column represents the average weight in milligrams of the adrenal glands per kilogram of body weight in control pigeons. This weight is approximately 93 mg. In pigeons that were fed on polished rice the weight of the adrenals reached as high as 160 mg.

The thyroid gland undergoes a considerable amount of atrophy in consequence of food deficiencies, so that their effect on one pair of organs—the thyroid and the adrenal—that are so intimately concerned with metabolic regulation, is to cause a diminution in the size of the former and an enlargement of the latter.

I will show another chart in order to emphasize a further point. This chart represents the effects on the thyroid and adrenal glands of pigeons of excessive feeding with mixed millet seeds, peas, and butter. In contrast to the effect of deficient feeding, the thyroid undergoes great enlargement, and the adrenals diminish in size. These organs are affected in a reverse order according as the food is deficient in certain essentials or excessively rich in other essentials. In the former case the adrenals enlarge and

the thyroids diminish in size; in the latter the thyroids enlarge and the adrenals diminish in size.

The next picture represents a section of the normal thyroid gland of a pigeon. It is one of the control pigeons referred to in the previous chart. Contrast it with this one which shows a section of the thyroid gland of a pigeon that was fed on a diet of mixed grains and butter. You will notice that the vesicles are almost filled with acinar buds, and that there is epithelial hypertrophy and scanty colloid. You will recall that this picture is one which is commonly recognized as characteristic of Graves' disease. Here is another one. You will notice here also that the acinar budding and epithelial hypertrophy are extreme and that colloid is scanty or absent.

Now we come to the effect of adding onions to this diet of mixed grain and butter. The effect of the onions is to reduce the incidence of the thyroid enlargement, the size of the actual goitre, and to alter, to a considerable extent, the histological picture from a hypertrophic to a more vesicular type. There is a considerable degree of congestion; the cells are not so high; acinar budding is much less pronounced, and there is rather more colloid in the vesicles. Here is another section which shows the same appearances. It would seem, therefore, that the histological character of the goitres produced in consequence of confinement, lack of exercise, contamination of the food and drink by fecal material, and over-eating of food excessively rich in fats, is capable of variation dependent upon the composition of the food eaten. This question of the effect of onions is a very interesting one, and very difficult to explain. It may be that their protective action against the hyperplasia induced by the excess of fats is due to the iodine-content of the onions. That I do not know, but I understand that a very small amount of iodine is present in onions, while some samples have none at all. On the other hand, it may have been due to their content of diffusible antiseptic. This antiseptic, as you know, has a wide repute in the treatment of purulent bronchitis. Onions are used by the native doctors of India in the treatment of cholera, and *succus alii* has a wide utility in

Western medical practice. It may be, therefore, that this antiseptic action came into play in the present instance. It is certain that the addition of onions to a dietary of mixed grains and butter would tend to alter the bacterial flora of the gastro-intestinal tract. Possibly their beneficial action may have been due to such an alteration; or it may be that all three of the possibilities I have mentioned were concerned in bringing about the beneficial result.

The more I work on the problem of the factors concerned in the production of goitre the less disposed am I to tie myself down to any single influence in its production. So far as simple goitre is concerned we must in the present state of knowledge take count both of nutritional and bacterial factors in its causation.

The next step in this study of the effects of fats on the thyroid was to ascertain what component of the butter gave rise to the thyroid enlargement. To that end I fed pigeons on a diet of mixed grains and oleic acid. The experiment was controlled by feeding at the same time other pigeons on mixed grains and butter, and others on mixed grains and cod-liver oil. This experiment was designed with the object of putting the animals under hygienic conditions favorable to the development of goitre. Two pigeons were confined in each cage, so that the amount of movement was very limited, and the fecal pollution of their food-supply was extreme. In this picture I show you the result of the experiment, which lasted 130 days. First of all you will notice the effect which non-hygienic conditions of life—lack of exercise, close confinement, contamination of food and water-supply by the animals' excreta—have in causing the enlargement of the thyroid gland. You will observe also that the addition of cod-liver oil to the food affords complete protection against these influences. Mellanby has noted the same effect of cod-liver oil in dogs. Next you will observe the effect of butter and of oleic acid in causing enormous goitres, especially in certain cases. In the case of butter the largest pair of thyroids weighed 950 mg., while the normal weight is approximately 25 mg. Both thyroids weighed rather less than one four-hundredth part of the total weight of the animal. This effect was produced by butter; it was also pro-

duced by oleic acid. The goitres produced by oleic acid are even larger. In one case the two thyroids weighed 1,050 mg., or considerably more than one four-hundredth part of the total body weight of the animal; so that I think one may reasonably say that whatever effect butter has in causing hyperplasia can also be produced, and with equal certainty, by the unsaturated fat-oleic acid. It would, therefore, seem that the injurious effect of the butter is due to its content of this acid.

Now we come to another matter. I desired to pursue the question of the relation of fats to thyroid hypertrophy somewhat further, and to examine it from the point of view of fat-excess and iodine intake. For this purpose I used tadpoles, since their sensitiveness to the influence of iodine might serve as an index of the harmful effect exerted by fat-excess on the thyroid gland. The first thing that I did was to find a food on which tadpoles would grow and flourish, and to which the fats to be tested could be added. A mixture consisting of caseinogen, 15 parts, white flour, 85 parts, and green pond weed, was found to serve these purposes. The flour-caseinogen mixture could readily be made up into pills, either with water or with the fats to be tested. These pills were dropped into the china vessels containing the tadpoles and were readily eaten by them. In the case of the cod-liver oil they ate greedily at first and but sparingly later in the experiment. The charts which I now show you represent the results of this experiment. The addition of cod-liver oil, butter, or oleic acid to the basal diet caused great retardation in the rate of the growth of tadpoles. The same effect was observed with lard, cocoanut oil, linseed oil, and arachis oil. This experiment lasted fifty-five days, and the actual weight of twenty tadpoles was plotted week by week. The next step was to ascertain what effect iodine would have when added to the diets that were excessively rich in fats. This chart represents the control experiment and shows the rate of growth of tadpoles receiving neither fats nor iodine, and of those receiving 0.5 and 1 mg. of iodine respectively per 3 gms. of food-mixture without fats. The next represents the rate of growth of tadpoles fed on a mixture containing oleic acid. This

dotted line represents the normal rate of growth in tadpoles receiving no oleic acid; the addition of 0.5 mg. of iodine almost completely compensated for the retardation of growth induced by the oleic acid, while 1 mg. of iodine did so completely. One mg. of iodine tended also to compensate for the retardation of growth induced by butter. In contradistinction to this compensatory action of iodine in the case of other fats, it will be noted that the addition of this amount of iodine did not compensate for the retardation of growth induced by cod-liver oil, but, indeed, further accentuated it. The more iodine one added to the cod-liver oil mixture the worse was the growth. I do not at the present moment wish to venture any explanation of these effects which, however, appear to be of much significance. It would almost seem that there is such a thing as a "fat-thyroid-iodine balance" and that a relative deficiency of iodine may be brought about in consequence of an excess of fat in the food and especially of the unsaturated oleic acid. If this be so it would provide an important example of a deficiency disease (goitre) due to want of one essential element of the food (iodine), resulting from excess of another essential food constituent (fat).

I have shown you the effects of deficient foods on the thyroids and adrenals of pigeons; it remains now to show the effects of deficient foods on animals more closely related to man. This chart shows the results of such foods as observed in monkeys. This column represents the normal weight of the adrenal glands in control monkeys; a diet which is deficient in all vitamins causes enlargement of the adrenal glands just as it does in pigeons. The thyroid atrophies, and there is a tendency to enlargement of the pituitary body, especially in males, just as there was in pigeons.

The next picture represents a cross-section of the adrenal gland of a healthy pigeon stained by osmic acid. It shows the normal proportion between the cortical and the medullary columns. The slide shows that in pigeons subjected to complete avitaminosis the cortical areas are greatly increased in consequence of the deficient food. There is at the same time a depletion of the cortical lipoids, as demonstrated by Cramer. I have shown that an in-

crease in the epinephrine content approximately proportionate to the increase in size of the glands occurs. This effect on the epinephrine content is seen in the blood pressure tracings from sheep. The next specimen is a section of a sympathetic ganglion attached to the suprarenal gland of birds. I show it to you in order to point out the degenerative changes that take place in the nerve cells of the ganglion in consequence of avitaminosis.

I find, gentlemen, that I have been talking for well over an hour, and that is quite long enough. I hope I have not kept you too long. It was by request that I inflicted the historical survey of my earlier work upon you, and as for my recent results I lay them before you so that you may for yourselves form your own opinion in regard to them. I have thought it best to present the facts as I observed them, and to refrain from attempting to interpret them, for, indeed, much work still remains to be done before their true significance can be appraised.

*Discussion:*

DR. MARINE: I really had not planned to say anything, but as Colonel McCarrison has been unkind enough to mention my name a number of times in connection with this work, I suppose I shall have to. It has been a great opportunity to hear a man talk who has really seen goiter. Most of us have never seen it. I have lived in the Lake basin about sixteen years, and I saw goiter there, but nothing remotely approaching what Colonel McCarrison has seen in the Himalayas. Truly that must be the most severe goiter district in the world.

I was interested in what Colonel McCarrison said about the morphology of the thyroid. Of course a great deal is written and heard about this, but I had hoped that medicine was over the stage of spending a great deal of time on the morphological variations in the thyroid. It is such a labile tissue that it may undergo morphological changes within twenty-four hours. It seems to me quite as labile as the blood tissue. To say that this change is typical of this disease, and that change of that disease I think is quite impossible, and I believe, although I have very few friends in that regard, that there are more people coming to that point of view.

Another thing which I did not know about before is that the incidence of endemic goiter in India bears no relation to the incidence of Graves' disease. In this country it does seem to bear a relation in a great many cases. Colonel McCarrison's explanation that Graves' disease is a disease of civilization is one that appeals to me. Both Graves' disease and simple goiter are increased in the Great Lakes district of our country. In the negro one rarely

sees exophthalmic goiter. I have seen several cases of it in mulattos. Colonel McCarrison's statement is interesting that Graves' disease is very rare in the natives in India, but may develop in those same natives when transported to the war zone.

The question of adenomas, the so-called toxic adenoma, is a very interesting subject. I have the feeling that the adenoma is of secondary etiological importance in the development of this peculiar syndrome or toxic picture. My experience has been somewhat similar to what Colonel McCarrison saw in India, that most endemic goiters eventually develop adenomas, and yet the incidence of toxic adenoma is exceedingly small. It seems to me that Graves' disease or toxic adenoma must be something more than the mere presence of an adenoma. That is the personal feeling I have.

Regarding the etiology of goiter, and with all due deference, I do not believe that water is the etiological factor. If water is related to goiter I believe it is due to the absence rather than the presence of something in it. On the other hand, the investigations which Colonel McCarrison has carried on with bacterial toxins seem significant to me, and there is no doubt there is some association when we remember that in infectious diseases the thyroid usually reacts. Why or how I cannot explain.

Another important point in the paper to-night is the observation that in inanition and in deficiency diseases in general the cortex of the suprarenal gland may undergo a most remarkable enlargement. That is a striking thing, but that is not all of it. The epinephrine content likewise is increased. I might digress just a moment to mention some recent work with the adrenal cortex. I have shown that if you cripple the adrenal cortex in a cat or a rabbit there is a remarkable increase in heat production which may last for months. That increase in heat production is associated with increased activity of the thyroid gland. If the thyroid gland is removed, and then the suprarenal cortex is crippled, you will not get increased heat production. There is some relation then between the suprarenal cortex and the thyroid gland which is a relatively new thing as compared with the older relation between the chromaphil system and the thyroid gland. In other words, epinephrine will stimulate the thyroid gland. I think Dr. Goetsch will accept that. If we have shown anything it is that the suprarenal cortex also plays a rôle in thyroid activity.

The last point brought out was really quite new to me until recently, that is, the relation of fat feeding to the histological evidence of thyroid activity. Looking back over the work I have done in the last sixteen years it seems to me that I can see confirmation of Colonel McCarrison's results. In fish, for example, brook trout would get goiter when fed with pigs' liver. I have seen chicken farms that had to be abandoned because of goiter. I have seen several dairy herds in the Lake region where nearly all the calves were cretins with huge thyroid enlargements and these were fed with cotton-seed meal in large quantities. All these facts further indicate that there is something in the observation. How it operates is what I would like to ask Colonel McCarrison, but he has forestalled that question by saying that he has no idea.

Colonel McCarrison has stated that oleic acid is very potent in producing

thyroid hyperplasia, but that the administration of iodine with it markedly decreased this effect of oleic acid. I would like to ask one question. Have you worked with a series of fatty acids from the completely saturated fatty acids through oleic on to those very unsaturated fatty acids? I would like to know the effect of iodine in relation to the degrees of unsaturation. This is all a very interesting question, and we have no idea what it may be due to. It may have something to do with thyroid function and with alterations in suprarenal function, and after all we are trying to develop some of these interrelationships. Many people think it is very simple—that all you have to do is to put a few animals in a cage, use a little imagination, and a new relationship is established. I would like to put in a protest against what I am pleased to call "Endocriminology," because I do think it is criminal that a subject with such great possibilities should be exploited both commercially and scientifically.

DR. GOETSCH: I want to express my thanks to Colonel McCarrison and assure him of the great interest I had in listening to his presentation. I am not in a position to discuss his paper because my experiences are not as a rule with the simple goiters. These very rarely come to the surgeon, and my work is almost entirely with goiters producing hyperthyroidism. I was particularly interested in what Colonel McCarrison said about the occurrence of adenoma in India, and its percentage as compared with this very large number of simple goiters. I have always felt that the adenoma had no relationship to the same etiological factors on which simple goiter seems to depend, because of the fact that adenoma is a new growth. It is a benign growth. It is always encapsulated, and if it is not encapsulated, it is not an adenoma. Until we know what the cause of tumors is, we cannot say anything about the cause of adenoma. Then too the adenoma as far as I know has not been influenced greatly by any form of treatment with which I am familiar. The adenomas which I have seen are those which are causing hyperthyroidism. On a histological basis I think we have reason to say that the adenoma is responsible for hyperthyroidism of itself, because if you submit them to a very careful study for the presence of mitochondria, you will find that in every case of an adenoma associated with hyperthyroidism, the cells are rich in mitochondria. These mitochondria are excessively abundant, and if a section is taken from the thyroid gland just beyond the capsule of the adenoma, one finds that the thyroid gland itself has a colloid structure, in which one finds very few or no mitochondria at all. I have taken an adenoma from the side involved, and a wedge of tissue out of the opposite thyroid lobe in which one finds the same picture, and it seems to me that the cells of the adenoma, showing thus histological activity, are responsible for the hyperthyroidism present. I have tried to explain this colloid change in the gland outside of the adenoma on the same basis that Dr. Marine has caused the thyroid hyperplasia in his animals to revert to a simple colloid picture following the administration of iodine. I believe that the adenoma furnishes a toxic body which is closely related to thyrotoxin, and which is present in the body fluids in excessive amounts, and that the normal thyroid as a consequence reverts to a simple colloid picture very different from that seen in the ade-

noma. I have felt that if we were able to go back into these individuals after the excision of an adenoma we would probably find that this resting thyroid which before had a very simple inactive looking picture with the absence of mitochondria and the presence of fat would again take on an active appearance. In a simple colloid goiter the cells are filled with fat, and there is the absence of mitochondria. After the excision of the adenoma I believe this resting thyroid comes back to the normal picture again. I do not quite understand what Dr. Marine meant by saying that these simple colloid goiters might develop through all stages to the formation of adenoma and finally fetal adenoma. I do not know whether you meant the formation of these encapsulated tumors that have no relation to the thyroid as such, that can always be shelled out, or whether you meant those hyperplastic more or less circumscribed areas which one often sees.

DR. MARINE: I was speaking of all degrees of encapsulation.

DR. GOETSCH: These adenomas always have a definite capsular structure separating them from the normal thyroid, and one can see even microscopic adenomas, and from them trace their evolution up to those large ones with a capsule one centimeter thick. That is the adenoma I meet in my work. Of course those adenomas that do not produce symptoms of hyperthyroidism will not come to the surgeon for treatment, except when they produce symptoms of pressure.

COLONEL MCCARRISON: Do you see a constant type?

DR. GOETSCH: We get every possible microscopic picture in adenoma, and I feel that being a tumor and arising from the fetal cells of the thyroid, it has the potentiality of developing into any histological type from the simple colloid to the higher degrees of hyperplasia resembling that seen in exophthalmic goiter. The fact that these fetal cells can reproduce any type of histological picture makes it very confusing and difficult to classify the adenomas. But when one applies the technique for the demonstration of mitochondria, then one finds that the simple adenoma without symptoms is relatively poor in mitochondria, and that the toxic adenoma, associated with definite symptoms of hyperthyroidism, is just as rich in these structures as exophthalmic goiter. If one applies the criterion of mitochondria one need not care whether the cells are tall or not, or whether there is much or little infolding. The presence or absence of mitochondria forms a better criterion of activity. In exophthalmic goiter the mitochondria are always present in large numbers. I have never had a case in which I have failed to find them. I have examined between three or four hundred. The adenomas are much more common of course.

DR. EWING: A countryman of Colonel McCarrison's said some time ago that medicine had passed beyond the descriptive stage, and was now engaged in quantitative measurements of the phenomena of disease. That may be true in certain very well known diseases, but we are still in the descriptive stage in thyroid diseases, and the observations which Colonel McCarrison has made illustrate the type of work by which successful research in this field may be conducted. I am greatly impressed by the ingenuity with which he carried on his work away out in northern India. It shows that when one

has the idea and the will the environment will lend itself. In regard to the practical aspects of this matter, I am extremely interested in the experiments with the thyroid and the adrenal, because they give one a new point of view from which to carry on work as a general pathologist. I have been looking at the adrenal for a good many years, without much intelligence, I must confess. We are getting information about the adrenal lately, and I find it possible to use a little more intelligence in the examination of this and the other endocrine glands at autopsy. I think in this way we are eventually going to get a basis on which to build up endocrinology and bring actual scientific facts to bear on many of these problems. I think the general pathologist has a function to perform here, so I want to thank Colonel McCarrison again and trust that his work will reach the fullest fruition.

DR. PAPPENHEIMER: It was not clear to me whether this hyperplasia of the adrenals is due to a specific deficiency of the accessory substances, or is merely an accompaniment of the wasting that one gets under those circumstances. Have you made any experiments in which the vitamine deficiencies were supplied, but in which the total food intake was insufficient? I should like to ask in this connection whether the cortical hyperplasia is due to a passive overloading of the cortex with lipoids mobilized during the process of acute inanition?

DR. OPPENHEIMER: I should like to ask what is the geology of that district in India, and just what is the history of the neighborhood.

COLONEL MCCARRISON: I do not propose to say much by way of reply except to answer the questions that have been put to me so far as I can.

As to the matter of the specific action of vitamins on the adrenal glands: An increase of the epinephrine content occurs in consequence of inanition. An increase of the epinephrine content occurs also in consequence of complete avitaminosis. No increase in epinephrine content appears to occur if vitamin A be supplied in the food. Associated with the hypertrophy of the cortex that results from avitaminosis, and coincident with the increased epinephrine content in the medulla, a depletion of the cortical lipoids occurs. Cramer has shown that the depletion of lipoids from the cortex is associated with the absence of vitamin A from the dietary. The absence of vitamin C produces some very curious effects. In guinea pigs fed on a scorbutic diet the adrenals are greatly enlarged; circumscribed areas of hemorrhage also occur in the cortex. I have never seen precisely this appearance in any other condition. The circumscribed areas of hemorrhage are distributed all around the adrenal cortex. The absence of vitamin A is associated with a great fall in the epinephrine content. The adrenal changes are among the earliest of the manifestations of vitamin C deficiency.

In regard to the question about the geology of the Gilgit district. I regret that I cannot rely on my memory at the moment for details regarding it. An account of its geology was kindly prepared for me by an eminent geologist who visited the district, and the matter is dealt with in my Milroy Lectures delivered before the College of Physicians of London in 1913. I would refer you, sir, to the original source for the answer to your question.

# TUMORS (3) OF THE KIDNEY PELVIS AND OF THE URETER

P. W. ASCHNER, M.D.

We are all familiar with the ordinary papillary tumors of the bladder, and with the usual types of carcinoma of the bladder, but we are not so familiar with, and do not see so often, these types of tumors in the kidney pelvis and in the ureter proper. Within the last year we have had three such cases.

The first of these was a man of fifty with hematuria, who on cystoscopy showed a very small papilloma at the neck of the bladder, which was destroyed by fulguration. However his bleeding continued, and another cystoscopy showed blood coming down from the left kidney. Nephrectomy was contemplated, but the man had a cerebral accident just before operation, and died. At autopsy the specimen was removed. It was a large kidney, the upper half of the pelvis showing a diffuse papillary growth, not of great thickness, not invading the kidney parenchyma, nor the submucous tissues. On section it proved to be an apparently benign papillomatosis of the renal pelvis. The other kidney was found to be extremely small and insufficient in tissue, so that had the contemplated nephrectomy been done the patient would probably not have survived.

The second case was another of left-sided hematuria in a man of sixty-two whose kidney was explored, and at operation was found to be a small and apparently nephritic one. Decapsulation only was done. A year and a half later, owing to the recurrence of the hematuria, he was again cystoscoped, and sticking out of the mouth of the left ureter was a small papilloma. We concluded that this was an implantation growth, the primary one presumably being in the renal pelvis. The kidney and ureter were removed The kidney contained in its pelvis a large tumor occupying the greater portion of the pelvis and its calices and invading the kidney parenchyma at the upper pole, with a number of small implantations along the course of the ureter. On microscopic section it proved to be a papillary carcinoma.

The third specimen is one from a man who had the typical history and signs of calculus disease of the right kidney. At operation a pyelotomy was done and the stones removed from the pelvis. At the site of the ureteropelvic junction a stricture was encountered. Because of the thickness of the tissue a small specimen was removed. We were much surprised to find that this was a squamous-celled carcinoma, primary in the ureter. The kidney and ureter were removed at a secondary operation immediately after the diagnosis was made. In addition to the ureter lesion, he had a very interesting condition. It was leukoplakia of the pelvis, chiefly in the lower of the two pelves which the kidney presented. The man has been well since except

that he has the leukoplakia in the bladder. The association of leukoplakia with cancer is well known in the tongue and the bladder, and I have looked through the literature and found no case of leukoplakia associated with carcinoma in the ureter. I am not convinced that it is on a leukoplakic basis *per se*. The ureter itself does not show a leukoplakic condition, and it is conceivable that he had a stricture at this point in his ureter, and that some of the leukoplakic material passed from the pelvis of the kidney, became caught at this point, and developed into a carcinoma.

I present these as three rather interesting unusual kidney tumors. It is interesting that fragments of the pelvic tumors are apt to break off and implant themselves in the ureter or the bladder. Such a growth in the bladder misleads one into believing that the bladder tumor is the cause of the hematuria. The case of squamous-celled carcinoma of the ureter is exceedingly rare. I have found only three in the literature, and of all primary tumors of the ureter, there are only about fifty on record.

*Discussion:*

DR. MACNEAL: I think it is a very interesting suggestion, made apparently without reservation, that secondary tumors arise in the ureter and in the bladder by implantation after transportation through the urine itself of particles of primary tumor from the pelvis of the kidney. The proof that implantation takes place in such a manner is rather difficult to furnish. I am not sure that it is generally accepted that this does occur. One has to think of other possibilities; there may have been perhaps a simultaneous development of tumors of the same type in various portions of the urinary tract. Also, one should perhaps think that the tumor may have metastasized through the lymph stream rather than through the lumen of the ureter itself. It is difficult to decide between these possibilities. The question of the implantation of tumors, especially the implantation of malignant tumors, or their metastasis by other routes than through the blood or lymph stream or by immediate contiguity, is unsettled in pathology.

Recently we have seen a case in which papilloma of the pelvis of one kidney was present, and this was removed. Some months later the patient returned and had a papilloma removed from the rectum. There was a difference of opinion between the surgeons in this case as to whether the papilloma of the rectum might not be regarded as in some way derived from the papilloma in the kidney pelvis. The histology of the second specimen was that of the usual papilloma which occurs in the rectum, and it did not resemble that in the kidney pelvis.

The tendencies which exist in epithelial surfaces to develop papillary tumors have to be recognized as a tendency which may be common to a considerable surface of the epithelium, and the question as to whether the second

tumor is an implantation of the first is a question about which we should keep an open mind in the present state of our knowledge.

DR. ASCHNER: The points made are very pertinent. We have a certain amount of clinical as well as pathological evidence that papillomata, particularly in the genito-urinary tract and probably in other parts of the body, can arise by implantation not through the lymphatics and blood stream. To my mind it is inconceivable that a papillary tumor at the neck of the bladder can come from the pelvis of the kidney by the lymphatics, because the lymphatic stream is in the other direction. I doubt if it would arise through the blood stream, because these tumors are very superficial things. It is not a malignant tumor in the sense of spreading by metastasis, but it can spread by implantation. In papillomatosis of the bladder that is true. You may observe a papilloma in the bladder near the ureter orifice and some time later see another at the fundus of the bladder. That is called a "kissing" lesion, for when the bladder is empty the fundus meets the trigone. The same thing is seen in tuberculosis of the bladder. We know that a bladder papilloma may be operated on, and all the tumors apparently removed; if the greatest precaution is not taken the patient may develop a growth in the suprapubic wound and along the course of the incision made in the bladder at the time of operation. That is one of the reasons why we cauterize the line of incision after the operation. I think these facts offer considerable evidence to show that papillary tumors of this type can implant themselves.

---

# ANEURYSM OF THE HEPATIC ARTERY

WILLIAM FRIEDMAN, M.D.

*(From the Pathological Laboratory of Mount Sinai Hospital, New York City)*

The patient, 57 years old, born in Russia, house-wife, was admitted to Mount Sinai Hospital on the service of Dr. A. V. Moschcowitz on July 16, 1921, with the following history:

Seven years ago she was operated upon for gall-stones at the Beth Israel Hospital. A cholecystectomy was done and the patient had an uneventful recovery. Six years ago she had an attack of severe colicky pain in the epigastrium radiating into the back and accompanied by vomiting which lasted for several days. During the week previous to her admission she had again suffered severe colicky pain in the epigastrium which radiated to the back. She had several such attacks during the week. Most of the attacks were accompanied by vomiting. Twenty-four hours before admission the patient noticed that she had become jaundiced. The only other important symptom in the history was nocturia for six weeks previous to admission.

The physical examination revealed an obese middle-aged woman, intensely icteric and acutely ill. There was marked tenderness and rigidity

over the entire right side of the abdomen, especially in the right upper quadrant, but no rebound tenderness. The liver was palpable 4 cm. below the costal margin on the right side. The edge was sharp, the surface smooth. There was a moderate leucocytosis and secondary anemia. The stool contained blood, but no bile. Blood Wassermann was negative. The blood chemistry showed urea nitrogen 56, incoagulable nitrogen 109. Her temperature varied between 99 and 100, and the pulse between 96 and 100. Respirations were 24.

Two days after admission the patient passed a large stool consisting entirely of old fluid and clotted blood. Her condition became worse and operation was decided upon. The operation was performed by Dr. Aschner. The omentum and transverse colon were found densely adherent to the abdominal wall and under surface of the liver. The intestines were plum colored. The common bile duct was found markedly dilated and when aspirated yielded a small amount of blood. Upon opening it several large blood clots were found. The right hepatic duct was probed and found free. The left hepatic duct when probed yielded profuse bleeding. Some obstruction was met in probing the common duct toward the papilla. A duodenotomy showed the papilla to be normal and a probe could be freely passed into the common duct. The surface of the liver showed no irregularities. A tentative diagnosis of carcinoma of the left hepatic duct was made. The patient died several hours after the operation.

Autopsy revealed a most intensely icteric middle-aged woman. The heart showed some irregular atherosclerotic thickening of the mitral cusps. There was also marked atherosclerosis of the aorta. The peritoneal cavity contained no free fluid. The liver weighed 1,830 gm. The gallbladder was missing, having been removed at a previous operation. On probing the right and left hepatic ducts a large amount of clotted and fluid blood exuded. Just posterior to the right hepatic duct was found a spherical aneurysm about 0.75 cm. in diameter. The aneurysmal sac was filled with an organizing thrombus which protruded through a defect in the right hepatic duct. The common and hepatic ducts and their smaller radicals were distended with blood throughout the entire liver. The intestines contained a great deal of old blood. Microscopically the hepatic artery and all its branches showed marked atherosclerotic changes. There was found a generalized atherosclerosis throughout all the medium-sized systemic arteries which were examined.

Up to June, 1921, there were fifty-four cases of hepatic artery aneurysm reported. The disease is more common in males. Grunert believes 75 per cent. followed acute infections. Rolland is of the opinion that as high as 20 per cent. are due to syphilis. Among other etiological factors are gallstones, and trauma at operation. There are two varieties: extra-hepatic and intrahepatic, the former being more common. It occurs most often in the main branch of the hepatic artery. They may be multiple.

Hoeglar believes that 50 per cent. of the aneurysms are mycotic in origin. Usually the vessels in the liver show thickening of the intima and media. Ledieu reported one case in which there was healing of the aneurysm. Death is usually due to rupture of the aneurysm into the peritoneal cavity, the biliary passages, the stomach or the duodenum. The pressure of the aneurysm on the biliary ducts is supposed to be the cause of jaundice.

In view of the history of this case, of an operation for gallstones seven years previously which was followed a year later by a severe attack of abdominal pain similar to the one which initiated the patient's final illness, the possibility must be considered that the aneurysm was due to weakening of the vessel wall as a result of trauma or of infection at the time of the operation. In view of the extensive general atherosclerosis throughout the body, in which the hepatic artery had proportionately shared, a weakening of the wall as a result of this process must also be considered. Investigation has revealed that there was no unusual trauma or infection at the time of operation and it would, therefore, seem that the aneurysm of the hepatic artery was due to an atherosclerotic change within the artery with subsequent rupture of this aneurysm into the right hepatic duct and death due to hemorrhage.

*Discussion:*

DR. G. A. FRIEDMAN: I was very much interested in the case of Dr. W. Friedman and in his excellent presentation of it. I would like to mention that about nine years ago I had a case in which I made a tentative diagnosis of aneurysm of the hepatic artery. A report of the case with operative findings was published at the time. I shall refer to the history later. The patient was operated upon by Dr. Arpad Gerster, April 9, 1912. These were the findings at the operation: "As soon as the margin of the lesser omentum was exposed, the artery became visible as a pulsating cylindrical body, having the diameter of a large goosequill. It formed a loop with its convexity downward. Its proximal continuation could be distinctly followed by palpation of the celiac axis, this forming a large loop with its convexity pointing upward, so that the whole vessel, as far as visible and palpable, represented a large Roman 'S,' its entire estimated length being six inches. A marked whirl could be felt on the gentlest contact with the vessel. The gallbladder was normal, moderately distended with bile, easily expressed into the common duct. The common duct was not distended and contained no stones, no palpable tumor, no cicatricial ulcer, absence of stone in the gallbladder.

"All the exposed structures, especially the duodenum, showed marked cyanosis, charged to the bad anesthesia. The margin of the liver was markedly rounded and thickened, free from cicatrices. The stomach was much dilated by gases which were withdrawn with a tube. The index finger could be easily invaginated into the pylorus." The division of the aorta into the iliacs, instead of corresponding to the fourth corresponded to the second lumbar vertebra. The calibre of the aorta and iliacs and the coronaries of the stomach was normal. "Diagnosis—Dilation and elongation of the hepatic artery. No aneurysm." I quoted in my paper Kaufmann, who says: "Dilation of an artery, also called arteriectasia, may be diffuse or circumscribed. Some authors call only the latter aneurysm, but this is in an error: there are transitions between the two forms."

Dr. Gerster himself called my attention several months later to an article which appeared in a journal, edited by Professor Garé, in which my case was quoted as follows:

"In a woman of about thirty-five years old, who gave a history of excessive use of alcohol, the following symptoms were noted: severe paroxysmal pain in the right hypochondrium which became more intense in prone position, visible pulsation over the region of the liver, a subjective sensation of throbbing in this area. Lower border of liver was palpable. Diseases like gallstones, duodenal ulcer, tumor, visceral arteriosclerosis, cirrhosis of the liver, aneurysm of the aorta were ruled out. A diagnosis of aneurysm of the hepatic artery was made and the diagnosis was confirmed through exploratory laparotomy."

Three years later Professor Alb. Narath of Heidelberg, in discussing in his paper the necessity of ligating the hepatic artery in aneurysm, refers to my case as follows: "What happened in Friedman's case should never occur again. One should not satisfy himself with an exploratory incision in this condition, simply leaving the patient to his fate." I believe therefore that my case was an aneurysm of the hepatic artery. What became of my patient I do not know. I saw her seven months after her operation: her complaints and the clinical picture remained practically the same as before the incision.

In concluding I would like to say a few words in regard to Dr. W. Friedman's paper. It is possible that his patient had already her aneurysm at the time when she was operated upon at The Beth Israel Hospital for gallstones, because in the literature cases are recorded in which gallstones and aneurysm of the hepatic artery were found simultaneously. That the latter condition has a chronic course, over a period of years, is known to anyone who has looked up the literature of the subject.

DR. ROSENTHAL: Were the other vessels in the case of Dr. William Friedman investigated in reference to periarteritis nodosa?

DR. WILLIAM FRIEDMAN: The vessels were investigated with that in view. Teacher and Jack about a year ago published a case of hepatic artery aneurysm and reported a lesion which looked very similar to the lesion found in periarteritis nodosa. In this case we found no such lesion.

# CALCIFICATION OF THE PERICARDIUM

A. WINKELSTEIN, M.D.

(*From the Pathological Laboratory, Mount Sinai Hospital, New York City*)

The specimen is the heart and the pericardial sac from a male patient 39 years old who was admitted to Mount Sinai Hospital in June, 1921. Ten years before, following an attack of rheumatic pain in the left arm, he was admitted to the Presbyterian Hospital with cardiac symptoms—chiefly dyspnea, palpitation, and edema of the lower extremities. He recovered in eight weeks and remained without symptoms until three years later, when he had a similar attack lasting five weeks. Following this he was well until two months before admission to Mount Sinai Hospital. His complaints then were dyspnea, cough, anorexia, weakness, epigastric pain, and edema of the lower extremities. The physical examination pointed to a cardiac decompensation due to aortic stenosis and mitral stenosis with insufficiency. Furthermore, on account of a continuous fever, irregular chills, and the occurrence of numerous white-centered petechiæ in both conjunctivæ and in the skin generally, an active subacute bacterial endocarditis was suspected. Four blood cultures, however, were negative. A broncho-pneumonia was also present. Three weeks later he went into a stupor and died. Briefly then, this case was one of cardiac insufficiency probably due to rheumatic valvular defects and possibly complicated by an active subacute bacterial endocarditis.

The post-mortem findings were very interesting. There was broncho-pneumonia, old right pleural adhesions, and an enlarged, granular liver, showing microscopically perilobular cirrhosis, and chronic passive congestion of the spleen, kidneys, and intestines. The coronary arteries and aorta were negative. The pericardium was universally adherent to the surrounding structures.

The heart with the pericardium weighs 1,100 gm. and appears like a huge cor bovinum. The visceral and parietal layers of the pericardium are universally adherent and thickened. In the region of the atrio-ventricular grooves the thickening amounts to several centimeters. Here it is densely infiltrated with lime so that a bony hard ring almost completely encircles the heart. This calcification extends for a distance of a few centimeters down on both ventricles and up on both auricles. On cracking open this ring small cavities are found in some places which are filled with cheesy, caseous material or thick pus. Both auricles are tremendously thickened and dilated. There is a moderate hypertrophy and dilatation of the right ventricle and a huge hypertrophy and dilatation of the left ventricle, the myocardium here measuring 3.5 cm. in thickness. There is a moderate stenosis of the tricuspid valve due to thickening and fusion of the cusps and a very marked mitral stenosis, the aperture of the valve admitting only the tip of one finger. The bases of the mitral valve cusps are infiltrated with lime. On the auricular aspect of the mitral valve, there are two irregular fissures covered with blood

platelet thrombus (the probable source of the petechiæ). The aortic cusps are so thickened, fused, and infiltrated with lime, as to form a moderate degree of stenosis as well as insufficiency. The myocardium is normal in color and presents grayish streaking.

The radiograph of the excised heart and pericardium reveals the calcification so exquisitely as to give one a false impression of overlying ribs.

Microscopically the pericardium shows a thick layer of scar tissue in some places and marked deposition of lime in others. Also within the calcified areas, scattered here and there, small areas of bone formation are found. There are also large areas of purulent infiltration which have a tendency to invade the myocardium. No tubercles are seen. The heart muscle is markedly hypertrophied and there is a moderate amount of perivascular and interstitial fibrosis. Bacteriologically, smears, cultures, guinea pig inoculation from the pus and tissue stains for the usual bacteria and for tubercle bacilli all proved negative.

Summarizing, the specimen shows:

1. A universal pericarditis externa.
2. An extensive adherence of the visceral to the parietal pericardium.
3. The presence of an old suppurative pericarditis with marked calcification and some ossification occurring chiefly in the atrio-ventricular region.
4. A tricuspid and mitral stenosis—an aortic stenosis and insufficiency.
5. Myocardial hypertrophy and dilatation.
6. A negative bacteriological study.

From the clinical and pathological findings in this case it seems fair to conclude, although this cannot be proved, that this man had, in the course of his ten years' illness, (1) an acute rheumatic fever, (2) rheumatic endocarditis resulting in his valvular defects, and (3) a complicating suppurative pericarditis with subsequent calcification and ossification, the exact etiological agent of the pericarditis being unknown.

On account of the rarity of such calcification and ossification and the unusual nature of the specimen it seems worth while to attempt to summarize briefly the available literature on the subject. Fritz Diemer in the *Zeitschrift für Heilkunde* first drew attention to this condition, describing in 1899 ten cases. In 1901 A. E. Jones in the *Transactions of the Pathological Society of London* collected and analyzed fifty-eight cases occurring in the literature from 1726 to 1897. In 1902 H. I. Wells reported four cases from Cook County Hospital. Simmonds of Hamburg reported in 1908 the X-ray diagnosis of such cases during life, and

in 1918 his assistant, E. F. Müller, added eight cases with a splendid critical discussion. These are the outstanding papers on the subject. The following points in these papers are of interest.

It is a very rare disease. Up to the present there are only seventy-five cases on record. It occurs three times more frequently in men than in women, and the age varies from twenty-nine to sixty-six years. The etiological agent in some cases was definitely the tubercle bacillus, in one case the anhemolytic streptococcus and, in another, old hemorrhage; occasionally a preceding rheumatic fever or pericarditis is mentioned. In fully two-thirds of the cases, however, the cause was not demonstrable.

The pathogenesis in these cases is not entirely clear. As you know, the course of a pericarditis is determined by the virulence and character of the infecting agent, the resistance of the individual, and the therapy applied. Depending on these factors one will find the outcome to be either (1) death of the patient or (2) complete restoration to normal or (3) more or less thickening of the pericardium or (4) adhesions—complete or incomplete—internal, external, or both, or (5) inspissated pus or blood or caseous masses—loculated or not. It is chiefly in such purulent, hemorrhagic, or caseous areas that lime deposition occurs. It occurs also occasionally in large areas of scar tissue or adhesions. Although the exact physico-chemical factors involved in calcification are not yet completely known, it is a general rule that wherever there are large areas of dead, dying, or hyalinized tissue, lime salts may be deposited.

One finds the following pathological features in these cases: (1) frequently a pericarditis externa, (2) an adherent pericardium —usually universal, and (3) calcification. This calcification is variously described in the form of granules or masses; plates in or between the visceral and parietal pericardium; irregular pieces extending into the myocardium; rings or bands (especially in the atrio-ventricular grooves), and rarely there is a complete enclosure or the so-called "cuirassed heart sometimes designated as the marble heart." A few cases are described where the calcification proceeds outward from the bases of the valves. Very rarely, as

in the case reported here, a partial ossification in the calcific areas may occur. The other organs often show changes. The heart may be hypertrophied and dilated—pleural adhesions are frequent and cirrhosis of the liver is mentioned in one-seventh of the cases.

Müller brings out the following points in the study of his eight cases: (1) The process nearly always commences in the pericardium over the right ventricle. (2) It is progressive. (3) It later extends to the left heart. (4) The cause is subacute and acts for a long period of time. (5) The tubercle bacillus and the anhemolytic streptococcus could act in such a manner, he supposes.

There is no definite clinical picture of this disease. In 25 per cent. of the cases there were no symptoms and in the others merely those of cardiac insufficiency. Although metallic murmurs and osteal percussion notes have been described, these seem to have been post-mortem retrospects. In 1908, Simmonds at Hamburg made the important observation that extensive calcification of valves, myocardium, or pericardium could be diagnosed during life by the X-ray. Since then Groedel, Schwartz, Weill, and Rieder have reported cases so diagnosed. Obviously, however, the diagnosis is only of importance in regard to the prognosis, since treatment is of no avail.

*Discussion:*

DR. ST. GEORGE: We had a case of calcification of the pericardium recently in Bellevue following an empyema which the patient had, and was operated for. The calcium deposited in the pericardium was torn during the attempted operative removal in such a way that it ruptured into the auricle and the patient bled to death. In this case the individual had no lesion anywhere in the endocardium. All the valves were normal. He had an adhesive pericarditis with this calcification which involved the pericardium on the side in which the empyema was, and also along the diaphragmatic surface.

There was no evidence of bone formation in this calcium.

*Bibliography.*

F. DIEMER. *Ztschr. f. Heilk.*, 1899, xx S., 247.
A. E. JONES. *Trans. Path. Soc. London*, 1901, lii, 181.
H. I. WELLS. *Amer. Jour. Med. Sc.*, 1902, cxxiii, 241.
E. F. MÜLLER. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1918, xxv, 231.
SIMMONDS. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, xx S., 371.

# 1. MULTILOCULAR ECHINOCOCCUS OF THE LIVER
# 2. HYDATID ECHINOCOCCUS OF THE SPLEEN

LEO EDELMAN, M.D.

*(From the Pathological Laboratory of the Mount Sinai Hospital, New York)*

The specimens which I have to present before the Society illustrate the two types of echinococcus found in man,—one, a multilocular or alveolar echinococcus of the liver and the other, shown mainly by way of contrast, a hydatid echinococcus of the spleen.

The first specimen was removed from a Russian woman, age 33, admitted to the surgical service of Dr. Berg, May, 1918. She entered the hospital complaining of pain, tenderness and discomfort in the right upper abdomen which had been present for about two months. There was no radiation of pain and no jaundice. In her past history she related that a mass was felt in that region by her family physician some two years before onset of symptoms but she declined operation at that time. This mass grew very slowly and only became tender a few weeks prior to admission to the hospital. On physical examination the patient appeared slightly emaciated, and presented a palpable mass just below the costal margin in the right upper abdomen which felt firm, nodular, and was freely movable with respiration, apparently attached to the liver. The blood picture and blood Wassermann were negative, as was the X-ray.

The patient was operated upon by Dr. Berg, who found a hard nodular mass intimately connected with the liver and overlying an apparently normal gallbladder. In the absence of any palpable metastases, he considered the condition a primary operable carcinoma of the liver and resected the tumor.

The excised specimen which was sent to the laboratory consisted of an irregular yellowish white, rather firm, nodular tumor mass measuring about 10 x 8 cm., roughly triangular on cross section with normal liver tissue at the base of the triangle. To the outer aspect of the mass, attached partly to it and partly to the liver tissue, was an apparently normal gallbladder. The cross section through the tumor presented a honeycomb appearance, the spaces containing cholesterin-like material with granular detritus simulating necrosis. The gross appearance of the tumor suggested the following possibilities: (*a*) Gumma of the liver; (*b*) Colloid carcinoma with ulceration and necrosis; (*c*) Multilocular echinococcus.

Under the microscope the diagnosis of multilocular echinococcus disease of the liver was established, although no hooklets were found. The stroma defining the characteristic alveolar spaces consists mainly of sclerosed connective tissue derived from the liver, granular detritus with remnants of de-

generated liver cells, leucocytic infiltration (round cell and polymorphonuclear) near the periphery, and alveoli containing greatly contorted and folded chitinous vesicles filled with plugs of colloid material. Some areas show caseation and coagulation necrosis resembling a gumma or solitary tubercle with perivascular infiltration.

The patient made an uneventful post-operative recovery and was lost track of after leaving the hospital.

The second specimen was removed from a young woman, age 26, a native of Poland, admitted to the surgical service of Dr. Elsberg, September, 1921. She entered the hospital complaining of discomfort in her left upper abdomen which had existed for about ten days. Nothing abnormal was detected by her family physician prior to this time. Her previous history was negative. On physical examination the patient appeared moderately well developed and presented a rather firm fixed mass in the left upper abdomen, which reached downward to the level of the umbilicus and across to the mid-line. The liver was not palpable. There was no jaundice. The blood picture and blood Wassermann were negative. The temperature was normal, and urine negative. X-ray of pneumoperitoneum (Oxygen) showed an enlarged spleen and small liver.

The patient was operated upon by Dr. Wilensky, who found the spleen to be the seat of a tense cyst, rather firmly fixed to the diaphragm, and which he removed after considerable difficulty. The liver was explored and found to contain a smaller cyst in the right lobe. This was left intact for a subsequent removal.

The specimen which was sent to the laboratory consisted of a spleen somewhat elliptical and rounded, about the size of a large grapefruit, almost entirely replaced by a cyst, leaving only a thin shell of splenic tissue. The cyst proper was of the typical hydatid variety, having a white chitinous thick-walled membrane, smooth on its outer aspect, and a yellowish jelly-like substance loosely attached to its inner surface. The latter was found laden with numerous scolices and hooklets. The fluid contained within the cyst had a limpid opalescent appearance.

The microscopic section shows the characteristic lamellated structure of the cyst wall with areas of calcification.

There seems to be some doubt as to whether the two types of cysts presented are caused by the same species of *Tœnia*. The multilocular echinococcus was originally regarded as a colloid cancer until Virchow, in 1856, showed it to be parasitic in origin. His opinion held sway up to comparatively recent years. The Russian authority, Melinkow-Raswedenkow, working in a region where this type is almost endemic, bases his advocacy of a duality of species on various grounds, such as its peculiar growth and reproduction, its reaction to containing tissues and its somewhat

restricted geographical distribution. Mangold and Müller, as a result of feeding experiments, maintain that they obtained from it a different *Tœnia,* evidenced by the appearance of the hooks and the distribution of the ova.

The cases of hydatid disease recorded in the United States were first collected by Osler (1882), Sommer (1895–96), Lyon (1902), and Magath (1902–1921). In all, there were 334 cases. Using the available data up to 1902, 91 per cent. occurred in foreign born, and 9 per cent. in natives. From 1902 to 1921 Magath found only four cases who were native born Americans and from the data he had at hand he could not conclude whether all or any of these patients travelled. Professor Osler refers to only six cases of multilocular disease of the liver reported in the United States, occurring chiefly in Germans. The specimen presented to this Society is the first that I could find in the records of Mount Sinai Hospital. The multilocular variety seems to be most prevalent in Russia including East Siberia, Bavaria, Würtenberg, the adjacent districts of Switzerland and the Tyrol, whereas the hydatid variety is most commonly found in Iceland, New Zealand, Australia, Argentina and Uruguay.

The parasite is most commonly located in the liver. Vegas and Cranwell in their review of 2,027 cases of hydatid cysts arrived at the following percentages: liver (74.9 per cent.), lung (8.5 per cent.), muscle (5.7 per cent.), spleen (2.3 per cent.). kidneys (2.1 per cent.), brain (1.4 per cent.), bone (0.9 per cent.), and various other organs (4.2 per cent.). Just how the larva enters the organ it infects is not clear. However, it seems that the larva hatches in the intestine, enters the blood stream, and stops in the organ where it happens to be arrested. The frequency of liver infection also points to a possible migration by way of the common bile duct.

*References*

MAGATH, T. B. "Echinococcus Disease: Etiology and Laboratory Aids to Diagnosis." *Med. Clin. of North Amer.,* Sept., 1921, pp. 546–571.

MELNIKOW-RASWEDENKOW, N. "Studien über den Echinococcus alveolaris sive multilocularis," 1901 (Bibliography).

OSLER, W. "Principles and Practice of Medicine," 8th ed., 1913, p. 293.
STIRLING, E. C., AND VERCO, J. C. "Hydatid Disease." *System of Medicine*, Allbutt and Rolleston, 1909, vol. ii, part ii, pp. 876–1039.
VEGAS, M. H., AND CRANWELL, D. J. "Hydatid Cysts." *Nelson's Loose Leaf Medicine*, 1920, ii, 434–452.

---

# TERATOID CYST OF THE HYPOPHYSIS

J. H. GLOBUS, M.D.

*(From the Pathological Laboratory of the Mount Sinai Hospital, New York)*

Among the cystic tumors found at the base of the brain there is a small group of cysts which are characterized by an inner lining of stratified squamous epithelium, and in which epithelial pearl-like structures, cholesterin crystals and occasionally bone are found. Through their attachment to some part of the pituitary body and because of their pressure upon the latter and the adjacent hypothalamic region, they frequently give rise to symptoms of pituitary disfunction and thus acquire in addition to histological interest a clinical significance.

Such tumors were often described as cholesteatomas, dermoids, epidermoids, and, because of occasional occurrence of cartilage or bone in their walls, they were also occasionally grouped with the teratomas.

This confusion in the classification of such cysts of the brain and its meninges was in part due to the fact that various incidental findings were accepted as fundamental features determining the character of such neoplasms. Thus the finding of the cholesterin crystals in such cysts led Mueller[1] to name them cholesteatomas, while Virchow[2] rejected this term, considering the cholesterin crystals simply an expression of a degenerative process, and preferred the old term of "Tumeurs Perlées."

For some time there was lack of agreement as to the origin of such tumors. Thus, Virchow believed them to arise from the pial connective tissue and by the process of metaplasia to gain their final histological features. Bonorden[3] thought that ectodermal

tissue at the time of its invagination and formation of the "Anlage" of the anterior lobe of the hypophysis was the source of origin of such neoplasms. Beneke,[4] however, maintained that the so-called meningeal cholesteatomata took origin from the endothelial lining of the meninges. He based his claim on the fact that he was able to demonstrate by the use of silver stain a strong similarity between the epithelial cells lining the cyst cavity and endothelial cells. Later,[5] however, he revised his opinion and had accepted in part the view that some of such cysts have an epidermal derivation, this being particularly true of those cysts which contain sebaceous glands and hair. Bostroem[6] studying in greater detail meningeal and dural cholesteatomata came to definite conclusions as to the nature and origin of such cysts. He decided in favor of their epidermoid character. Erdheim[8] followed him by directing attention to a limited group of cysts which presented certain features in common, namely that they are always found at the base of the brain, in intimate connection with the pituitary body, are lined by stratified squamous epithelium and frequently contain cholesterin crystals. He traced the origin of such cysts to the embryonal rests of the subinvoluted cranio-pharyngeal duct. The latter, which is the "Anlage" of the anterior lobe of the pituitary body, does not undergo complete involution, but leaves behind small groups of epithelial cells which can be normally found on the surface of the anterior lobe of the hypophysis. These cells often give rise to tumors of the character here described. Erdheim suggested the term hypophysial duct squamous-cyst-papillomata for such tumors and separated them from the epidermoid cysts of Bostroem by pointing out some differences in their gross anatomical relationships and histological features. The epidermoids of Bostroem being true derivatives of the skin give uniformally the kerato-hyaline granular reaction in the epithelial lining and often contain hair follicles and sebaceous glands. In the hypophysial duct tumor, no kerato-hyaline granules, no sebaceous glands and no hair follicles can be demonstrated. Then again, the hypophysial duct tumors are always found in the midline at the base of the brain, back of the optic chiasm in intimate

relation to the diencephalon, while the epidermoids of Bostroem may occur in any part of the brain and its meninges, and present no relation to the pituitary body.

Since Erdheim's publication of his work a number of hypophysial duct cystic tumors were reported.

D'Orsy Hecht[9] described a so-called teratoma of the hypophysis in which he found bone and epithelial structures which he considered to have been derived from the anterior lobe of the hypophysis. It would seem that the failure to find any evidence of tissue derived from entoderm would not permit his case to be included with the teratomata as the latter are by definition trigerminal in origin.[7]

Jackson,[10] Canavil and Jackson[11] and finally Duffy[12] described a number of similar tumors and have come to the conclusion that they were derived from the misplaced remnants of the ectoderm which was destined to form the anterior lobe of the hypophysis.

The case herewith reported is of interest because it presents features characteristic of the hypophysial duct neoplasms described by Erdheim. It also shows the presence of hair germs, kerato hyaline granules in the lining epithelium and sebaceous cells. Thus it appears to represent a neoplasm with structures common to both the hypophysial duct tumors of Erdheim and the epidermoid cysts of Bostroem. It would seem that there hardly can be a well-defined line of demarkation between these two groups of cysts, for apparently they have a common stem of origin.

*Case L. P.* No. 210957. The patient was a girl, six years of age, who had had no previous illness, and who had been quite normal up to the time of the onset of symptoms, six months before admission to the hospital. At that time she became markedly constipated; her sleep was disturbed; she became restless and lost her appetite and would experience constant thirst, demanding water very frequently. Several weeks later, on consulting a physician, the diagnosis of diabetes was made and the child was treated accordingly. With the increase of thirst and increase of water intake, there was too an increase in volume and frequency of urination. The child was losing strength, and would frequently complain of fatigue; she gave up playing, became irritable, and finally became confined to bed because of constant headaches and general weakness. A week before admission it was noted that the child's mouth was

drawn to one side, and her left shoulder drooped and would frequently twitch. She was admitted to the hospital with the complaint of headache, fatigue, excessive thirst, enuresis, loss of appetite and weakness of the left shoulder.

Physical examination showed a fairly well nourished child, somewhat undersized, with a profuse growth of lanugo hairs all over the body, presenting no evidence of acute illness or mental deterioration. There was ptosis of the rght eyelid; external strabismus of the right eye due to weakness of the right internal rectus; the left pupil was larger than the right; both pupils reacted to light and accommodation. There was left facial weakness, and slight weakness of the left arm and hand; the latter was held in hemiplegic attitude. There was slight weakness of the left leg. The deep reflexes were more active on the left side, though generally reduced. There was a questionable Babinski, but gait and station were normal. The abdominal reflexes were not elicited. Spinal fluid was negative as regards cells and Wassermann. The diagnosis of neoplasm involving the posterior lobe of the pituitary and the right crus cerebri was made. The absence of distinct Babinski and the difference in abdominal reflexes indicated that the lesion was outside the substance of the peduncle.

*Autopsy Findings.*—(Examination of the brain only permitted.) On opening the cranial cavity the exposed dura was found to be normal in thickness and without demonstrable epidural or subdural hemorrhages. The underlying pia-arachnoid was markedly edematous and, because of the congestion of the arachnoid vessels, had acquired a purple hue. The cerebral hemispheres on the dorso-lateral surfaces showed evidence of increased intracranial pressure, the convolutions being definitely flattened and compressed. On raising the orbital surfaces of the frontal lobes, in the course of the removal of the brain from the cranial cavity, a large purple fluctuating mass presented itself at the base of the brain. It covered the optic chiasm and was adherent to the latter. Posteriorly it filled up the entire interpeduncular space. Its bulging inferior surface, which was partially free, was prolonged into a funnel-shaped process which seemed to be continuous with the pituitary body. The latter was extremely small in size, compressed, and was lodged in a shallow and eroded sella turcica. The base of the superior surface of this mass was firmly implanted in the substance of the basal surface of the brain. It occupied the entire intra-peduncular space, and because of pressure on the adjacent structures, the optic chiasm and tracts were flattened.

The tuber cinereum and the mammillary bodies could not be identified since the floor of the third ventricle was stretched and flattened by the tumor mass which almost obliterated the cavity of the third ventricle by its protrusion into it. The cerebral peduncles were displaced laterally and due to pressure were reduced in size; this was particularly pronounced on the right side. During the process of detachment of the brain from the base of the skull, the neoplasm was punctured and a dark-brown, granular, semi-fluid mass was found escaping from the cavity of the neoplasm. On opening the latter more fully, it collapsed and it was then noted that it was a rather thin-walled cyst, lined by a corrugated membrane which was beset irregularly by numerous small, glistening elevations. Cholesterin crystals were demonstrated in the

contents of the cyst by the employment of specific tests. The cyst measured about four centimeters in long diameter and about three and a half centimeters in width. By its expansion and central location it had stretched markedly the vessels constituting the circle of Willis, particularly the posterior communicating and anterior cerebral vessels.

Of the cranial nerves, besides the second, the third nerve on the right side was also compressed and flattened by the neoplasm. A horizontal, longitudinal section of the brain gave a still better view of the gross structural changes that were brought about by the neoplasm. The displacement and compression of the cerebral peduncle were brought well into view and the protrusion of a cyst into the third ventricle, practically obliterating the structures on the floor, was well shown. The cavity of the cyst was fully exposed and its inner wall was disclosed. The lining of the cyst gave the appearance of a mucous coat. At the left of the anterior portion of the cyst the wall was thickening, giving rise to a tuberous elevation, cartilaginous in consistency, and somewhat translucent in appearance.

*Microscopic Anatomy.*—In general the wall of the cyst was for the most part uniform in thickness and showed also a more or less uniform histological structure. It was composed of three layers. The innermost coat, a layer of stratified squamous epithelium, showed at a few points some little variation in the character and maturity of its epithelium. The middle layer consisted of loose connective tissue in which were imbedded numerous glandular acini and many small ducts. The glands were strongly suggestive of being salivary in character and the ducts were lined by tall cuboidal epithelium. The lumen of these ducts was filled with a pink staining colloidal substance. The third and outermost layer was composed of a fairly thin stratum of dense fibrous connective tissue, forming a boundary between the brain tissue and the cyst as well as the outer protective wall of the exposed part of the cyst.

A careful study of this lining epithelium showed its strong resemblance to the epithelium of the dermis of a young embryo. It consists of three layers, the outer corresponding to the epitrichium, the middle intermedian layer and the lowermost, the stratum germinativum. Here and there larger collections of cells composed mainly of the germinal layer gave the appearance of hair anlages, or hair germs. Another feature of interest was the accumulation of deeply staining epithelial cells arranged in concentric layers, giving rise to structures not unlike epithelial pearls. The cells in the center of these pearls appeared to undergo degeneration, the peripheral cells having retained the structure of basal-cell epithelium and showed, when stained specifically, the characteristic intercellular bridges; when stained with Weigert's method, a blue color was imparted to these cells giving evidence of the presence of keratohyaline. These collections of epithelial cells were on the free surface of the cyst, and were responsible for the small elevations that have been noted on gross examination of the tumor.

In the small cartilaginous mass in the wall of the cysts there were found several types of embryonic tissues of mesodermal origin such as embryonal cartilage, mucous connective tissue, young fibrous tissue, newly formed bone with typical bone corpuscles, calcified trabeculæ, endosteum and periosteum

crowded with numerous osteoclasts, osteoblasts, osteophites, and marrow cells, filled with yellow granules which on staining with specific methods gave a typical iron reaction. In addition to these structures, there was a collection of cells arranged in long cords and supported by a fine reticulum of connective tissue. The cytoplasm of these cells was reticular in structure with the fat apparently washed out. In frozen sections, stained by specific fat stains, the cells appeared filled with large fat globules. The pycnotic character of the nuclei and the irregularity in the fat globules gave them the character of cells in sebaceous glands.

## SUMMARY OF THE ANATOMICAL FINDINGS IN THE TUMOR DESCRIBED

The tumor was centrally situated, of the type of unilocular cyst, and was filled with dark-brown, coarse, granular material in which cholesterin crystals were found. Its interior was lined by corrugated mucous membrane on the surface of which were yellowish glistening papillary elevations. It bore a very intimate relationship to the hypophysis, being apparently attached to the infundibular process. Microscopically, it presented the following important features: It had a stratified squamous epithelial lining, which was embryonal in character. Here and there on the surface of the epithelial lining there was a heaping-up of cells which had a concentric lamellated arrangement, giving it the appearance of epithelial pearls. The latter were in various phases of degeneration, showing central areas of calcification, and were frequently surrounded by foreign-body giant cells. Alternating with these epithelial pearls, there were also found hair germs. Beneath this epithelial lining there was a connective tissue stroma, in which glandular tissue, salivary in character and in other places sebaceous in character, were found.

This tumor also contained embryonal cartilage, embryonal fibrous tissue, embryonic mucous connective tissue, and finally bone. The bone showed the characteristics of well-formed bone with its periosteum, endosteum, marrow cells, osteoclasts, osteoblasts, etc. It is quite conceivable in spite of all the earmarks of newly formed bone derived from misplaced bone "Anlage" that this tissue has developed by metaplasia through the degenerative process in the epithelial pearls, but it is unreasonable to

believe that the cartilage tissue, the mucous embryonic tissue, the salivary gland alveoli and sebaceous cells were all and each an expression of a degenerative process. It is most probable that they were elements derived from the two germ layers, ectoderm and mesoderm, which go to make up the mature skin. Thus we may assume that we are dealing here with an autochthonous teratoid growth derived from the elements concerned in the formation of the skin and that a misplacement of such cells from the two germ layers during the period of the invagination of the ectoderm in the course of the development of the hypophysis has laid the basis for the formation of the above-described tumor.

The failure to find hair follicles or sebaceous glands in the tumors described by Erdheim as hypophysial duct tumors is, perhaps, to be ascribed to the fact that such structures have escaped recognition because of their early embryonic character.

It is also evident from the reported findings by Duffy the presence or absence of kerato-hyaline granules cannot be looked upon as an important point of differentiation between epidermoids and cysts derived from hypophysial duct, as frequently poor and prolonged fixation may interfere with the kerato-hyaline reaction.

*References*

1. MUELLER, JOHANNES: Ueber den feineren Bau und die Formen der krankhaften Geschwulste. Erste Lieferung, 1838, p. 50.
2. VIRCHOW, RUDOLPH: *Virchows Arch. f. path. Anat.*, 1855, viii, 371.
3. BONORDEN: *Beit. z. path. Anat. u. allg. Path.*, 1892, xi, 593.
4. BENEKE: *Virchows Arch. f. path. Anat.*, 1895, cxlii, 429.
5. BENEKE: *Ibid.*, 1897, cxlix, 95.
6. BOSTROEM: *Centralbl. f. allg. Path. u. path. Anat.*, 1897, viii, 1.
7. WILMS: *Beitr. z. path. Anat. u. z. allg. Path.*, 1896, xix, 233.
8. ERDHEIM, J.: *Sitzungsber. d. k. Akad. d. Wissensch.*, 1904, Bd. cxiii, Heft. 10, Abt. III.
9. HECHT, D'ORSAY: *Jour. Am. Med. Assn.*, 1909, liii, 13.
10. JACKSON, HARRY: *Ibid.*, 1916, lxvi, 1082.
11. KANAVIL AND JACKSON: *Surg., Obst. and Gynec.*, 1918, xxvi, 61.
12. DUFFY, W. C.: *Ann. Surg.*, 1920, lxxii, 537.

# A CONTRIBUTION TO THE PATHOLOGY OF SUBACUTE EPIDEMIC ENCEPHALITIS

J. H. GLOBUS, M.D., AND I. STRAUSS, A.M., M.D.

*(From the Pathological Department, Mount Sinai Hospital, New York City)*

In the literature we find abundant and accurate descriptions of the neuropathological findings in acute epidemic ("lethargic") encephalitis. Following the lead of Von Economo[1] a large number of investigators—Marinesco,[2] Bassoe and Hassin,[3] Wegeforth and Ayer,[4] Neal,[5] and others—have recorded their observations on the gross and microscopic changes in the central nervous system caused by this disease. In their accounts of the lesions found in acute epidemic encephalitis, they refer generally to anatomical changes common to and characteristic of the acute form of the disease which are universally expressed in terms of perivascular infiltrations, a moderate amount of neuronophagia, a mild degree of glia proliferation, and occasionally hemorrhagic foci. It is further emphasized by them that the above changes are most commonly and most constantly found in the region of the midbrain and basal ganglia, not, however, to the complete exclusion of lesions in other parts of the central nervous system. Thus, lesions in the cerebral cortex (Hassin),[6] spinal cord (Calhoun),[7] and peripheral nerves (Burrows)[8] have been described as occurring in acute epidemic encephalitis.

However, it is quite evident that, in spite of their abundance, the above-quoted observations do not exhaust the subject of the histopathology of acute epidemic encephalitis.

Von Economo[9] has already reported a case which he called "chronic intermittently progressive lethargic encephalitis." His patient insidiously developed an atypical form of lethargic encephalitis which was characterized by alternate episodes of delirium and lethargy, dysarthria and slight pyramidal tract involvement. This condition remained unchanged for two months, and was followed by partial improvement. Later in the course of the

disease there developed dysphagia, paresis of the tongue leading to gradual debility of the patient and terminating in death a year and a half after the time of the onset of the disease.

Von Economo concluded that his patient was suffering from a chronic epidemic encephalitic process, to which new features were added in the terminal stage of the disease.

The anatomical changes which were associated with the lesions incurred during the early, acute period of the disease were (*a*) areas of softening with or without accumulations of granular cells; (*b*) bands of dense glia fibers; (*c*) small collections of glia cells, apparently cells which were at one time concerned with the process of neuronophagia; and finally (*d*) mild degenerative changes in the axis cylinders of long projection tracts. Among the new features he emphasizes recent perivascular hemorrhages, degenerative changes in ganglion cells, and perivascular infiltrations. He suggested that the recrudescence of the disease was probably due to incomplete elimination of the virus during the early period of the disease, and that a highly suggestive analogy was thus established between chronic progressive muscular atrophy in its relation to acute anterior poliomyelitis and this chronic form of lethargic encephalitis in its relation to acute epidemic encephalitis. It would appear from the clinical history of von Economo's case that an attempt towards healing must have occurred in the course of the disease, and it was apparently his aim to demonstrate this fact, but his histological descriptions fail to show any reparative change in the brain—the lesions described such as softening, accumulation of granular cells and extravasations pointing mainly to a lesion of destructive character.

In this regard, the findings in the group of cases reported in this paper demonstrate an important departure from the observations of von Economo, for we are in a position to demonstrate changes in the central nervous system that mark a well-defined tendency toward repair.

This series of cases might clinically be grouped with the mild protracted forms of lethargic encephalitis and could be termed subacute epidemic encephalitis. Early in their course they showed

a well-defined tendency toward recovery, then remained stationary for a variable length of time, finally to suffer a new insult leading into the acute, rapidly fatal, virulent form of the disease.

The important feature of this group of cases is the changes found occurring in the small cerebral vessels, indicative of an attempt on the part of the vascular system to repair the damage which occurred during the acute stage. The exacerbation of the disease, however, damaged the blood vessels, arrested the progress of repair, and this phase of the healing process became fixed.

*Clinical Observations:* It is not our aim to give a detailed account of the various clinical manifestations which have been observed in each of the four cases studied. A summary of the more constant and outstanding features common to all members of this group will be given. All of the patients studied have given a history of having had at one time a mild form of influenza in the course of the year preceding the onset of the apparently acute symptoms. They were admitted to the hospital complaining of general weakness, a variable amount of paresis and mild ocular symptoms. The clinical course during their residence in the hospital was marked at first by a tendency toward recovery, and improvement in their subjective and objective symptoms. This improvement, however, did not progress very far, and the condition became stationary. It is during this period that there occurred a sudden change; the patient became suddenly acutely ill, giving evidence of marked dyspnea, complete ocular palsies, dysphagia, and dysarthria. This apparently was the fatal turning in the course of events, as death took place soon after the onset of the acute recrudescence of the disease.

These striking features in the clinical course were paralleled by the anatomical changes to be described. It will be seen that lesions expressive of the three phases above noted in the clinical course of the disease can be demonstrated in the pathological material studied. Thus we shall find changes which are indicative of the early mild stage alongside of lesions suggestive of the reparative tendencies, and finally areas of destructive processes mark the final acute and fatal outcome of the disease.

*Autopsy Findings:* The gross anatomical changes consisted mainly of extreme congestion of the pial vessels, particularly over the ventral surface of the medulla and pons. No definite meningeal hemorrhages were noted in any of the four cases. Small petechial hemorrhagic foci, however, were seen on sectioning of the brains. The larger vessels at the base were followed out in their course to the smaller branches, and no arteriosclerotic changes could be found. The consistency and topography of the brains examined showed no abnormalities of note.

*Microscopic Findings:* In the course of the histological studies, a thorough search was made for minute anatomical changes throughout the brain stem, cerebral and cerebellar cortex. Particular care was exercised in the examination of the sections from the mid brain, basal ganglia and medulla, as the more important changes were anticipated there.

In general, it may be said, and this is highly significant, that lesions typical of the acute form of epidemic encephalitis were not conspicuous; nevertheless, in the vicinity of the aqueduct of Sylvius and in the medulla vessels were found showing the typical small round cell, adventitial infiltration. The most frequent findings throughout the brain stem were numerous perivascular and extravascular hemorrhages. That these hemorrhages were not agonal was shown by the presence of blood pigment in the adventitial spaces of blood vessels in parts remote from the seat of the extravasation of blood. Wherever such hemorrhages have occurred the walls of vessels involved showed no thickening or perivascular infiltration. Apparently these vessels were spared in the first attack of the disease and during the exacerbation of the disease the adventitia of these vessels was damaged to such an extent that it was incapable of proliferative changes and could not withstand the pressure of vascular engorgement. These hemorrhages were most extensive and most frequent in the medulla, this being noteworthy in its bearing on the clinical course of the disease. Another frequent finding was the small

accumulations of glia cells in groups of five or eight cells about ganglion cells undergoing neuronophagia.

Further evidence of an extensive degenerative process in the brain was found in the wide distribution of fat granules and globules in the cells of the adventitial coat of the vessels throughout the brain stem, and to a slight degree in other parts of the central nervous system.

Glia changes were also expressed as mild forms of proliferation and mobilization about blood vessels, in the subependymal layer in the floor of the fourth ventricle and of the aqueduct of Sylvius, and in the accumulations already described above. Only arterioles and capillaries were apparently singled out by the glia cells in their proliferative aggregation, and this fact coupled with adventitial changes in the smaller vessels constitute the most important pathological changes observed.

It was already pointed out that only close scrutiny yielded here and there a vessel with typical perivascular infiltration amid widespread perivascular and extravascular hemorrhages, while organization in the adventitial coat of the smaller vessels and capillaries was the most obvious and generalized change in the structure of the involved areas of the brain stem.

Apparently the perivascular, lymphocytic infiltration, which is the early anatomical manifestation of the disease, here gave place, through the proliferation and metamorphosis of lymphocytic elements and adventitial cells, to fibroblasts which thickened considerably the walls of the vessels. Further advance toward a distinct periarteritis was made through the progress of the same process of metamorphosis of the elements of perivascular infiltration. This is apparent in the thickening of the adventitia which is extremely rich in fibrous elements, though numerous lymphocytes are still found in the fibrous meshwork.

More striking, however, are the changes in the small capillaries of the involved areas, particularly in the gray substance about the aqueduct of Sylvius. They are expressed in the swelling and proliferation of the adventitial cells and the swelling of the intimal endothelial cells. This feature was often so pro-

nounced as to obliterate almost completely the lumen of the vessel.

Small vessels which are only moderately thickened were seen frequently surrounded by glia cells, a few lymphocytes and an occasional granular cell.

Microscopic examination of the vessels aided by specific stains such as resorcin-fuchsin, Van Gieson and Sudan III disclosed no features pointing to arteriosclerosis. Elastic membranes were intact; there was no splitting of the latter, no deposits of hyalinizing placques and no calcification in the intima or media.

The pia-arachnoid appeared normal except in a few small areas where it was distinctly thickened and presented features of organization such as the presence of many fibroblasts, small, newly formed blood vessels and lymphocytes.

*Significance of the Histological Changes:* It is evident that the modification of the structure of the small vessels forms the essential pathologic change. We believe that the primary attack of the virus is upon the wall of the small and medium-sized vessels, and that the vessel wall is affected by the virus in a manner proportionate to its virulence.

It is our opinion that many of the elements of the perivascular infiltration have their ultimate origin in the Virchow-Robin's space—cells often referred to by other writers as endothelial cells. These cells, characterized by a large amount of cytoplasm and clear vesicular nuclei, were found to be the predominating element in our preparations, and were frequently found in various stages of cell division.

It appears to us, then, that production of elements of infiltration, destined perhaps to repair damage occurring in the immediate vicinity of the vessel, is an important function of the adventitia. Thus, when the virus or even a mineral poison reaches the adventitia, it reacts by formation of adventitial elements, provided that the vessel wall is not damaged to an extent of losing its potency for adventitial proliferation. Should the virus or toxin, however, be so destructive to the vessel wall as to in-

capacitate it for cell proliferation and weaken it so it could not withstand the pressure of vascular engorgement, then perivascular hemorrhages will occur in large numbers, a feature characteristic of the acute, virulent type of the disease.

The reverse is also true, for when the virus reaches the vessel in a small amount or in attenuated form, changes pointing to subacute lesions follow, as was shown in our case.

Such interpretation of the histologic changes in the brain led us to suggest the grouping of acute epidemic encephalitis into:

1. An acute infiltrative form, with the dominant feature of perivascular infiltration.

2. An acute hemorrhagic form, where the virulence of the disease is expressed in numerous extensive hemorrhages.

3. A subacute productive form, as described in this paper.

The acute infiltrative is the early stage of any acute form of acute epidemic encephalitis which may resolve itself rapidly into the fatal hemorrhagic type or the protracted, mild productive form.

*References*

1. von Economo, C.: *Wien. klin. Wchnschr.*, 1917, xxx, 581.
*Ibid.*, 1918, xxxi, 850.
2. Marinesco, G.: *Bull. de L'Acad. de Méd., Par.* lxxx, 411.
3. Bassoe, P., and Hassin, G. B.: *Arch. Neurol. and Psychiat.*, 1919, ii, 24.
4. Wegeforth, P., and Ayer, James B.: *Jour. Am. Med. Assn.*, 1919, lxxiii, 5.
5. Neal, J. B.: *Arch. Neurol. and Psychiat.*, 1919, ii, 271.
6. Hassin, G. B.: *Jour. Nerv. and Ment. Dis.*, 1921, liii, 27.
7. Calhoun, H. A.: *Arch. Neurol. and Psychiat.*, 1920, iii, 1.
8. Burrows, M. J.: *Arch. Int. Med.*, 1920, xxvi, 477.
9. von Economo, G.: *München. med. Wchnschr.*, 1919, xlvi, 1311.

# Volume XXI, 1921

## INDEX

T



U



W



Y



Z